TABLE V. Correlation of Cardiac Measurements and Total Dose of THP

Measurements	Correlation coefficient	*P*
FS	0.01	0.09
EF	0.90	0.49
E/A ratio	0.08	0.57
CVNN	0.26	0.08
6MWT	0.02	0.88
BNP at rest	0.11	0.42
BNP after exercise	0.27	0.03

THP, pirarubicin; FS, fractional shortening; EF, ejection fraction. CVNN, co-variance of NN intervals; 6MWT, 6-min walk test.

was observed for subjects with $\geqq 300$ mg/m^2 of THP, but not for subjects with <300 mg/m^2 of THP. Although correlations between the measurements of left ventricular function (FS and EF) and cumulative THP dose or BNP levels were studied, no significant results were obtained (Supplemental Appendix).

DISCUSSION

THP is a derivative of DOX developed in Japan, and its cardiotoxicity may be lower than that of DOX [12–15]. Tsurumi et al. and Niitsu et al. reported that acute cardiotoxicity with THP was less frequent than that with DOX among adult lymphoma patients [17–20]. However, no studies for late cardiotoxicity of THP have been reported. In this study, cardiac function and biomarkers were measured in long-term survivors with ALL who received THP treatment and in whom no apparent cardiac dysfunction was detected. Thus, this is the first report of late cardiotoxicity of THP in cancer survivors.

The incidence of AC-induced cardiac dysfunction in childhood cancer survivors varied considerably across studies. The incidences of 14–24% for cardiac dysfunction assessed by echocardiography had been reported in five studies, in which median doses of cumulative AC ranged from 165 to 450 mg/m^2 [6,7,28,29,31]. Three other studies also reported that cumulative AC dose was significantly associated with reduced FS function, and high cumulative dose >300 mg/m^2 increased the risk of cardiac dysfunction [11,26,27]. When our results are compared with these findings, it appears that incidence of cardiac dysfunction after THP treatment

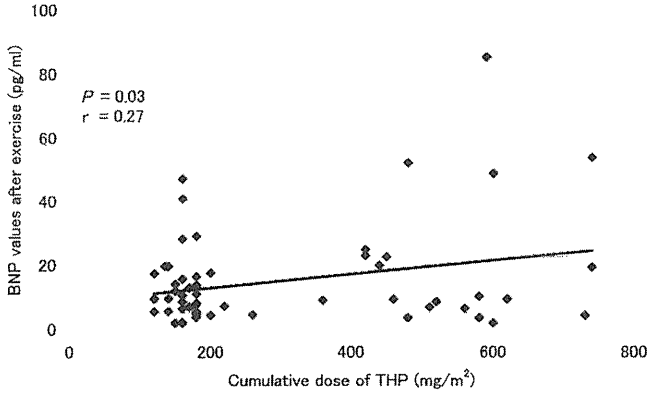

Fig. 1. Correlation between plasma BNP values after exercise and cumulative pirarubicin (THP) dose.

TABLE VI. Plasma BNP Levels According to Total Dose of THP

Total dose of THP	<300 mg/m^2 (n = 39)	$\geqq 300$ mg/m^2 (n = 21)	*P* value vs. <300 mg/m^2
BNP at rest (pg/ml)	12.5 ± 13.8	14.8 ± 15.8	0.56
BNP after exercise (pg/ml)	12.2 ± 9.9	20.6 ± 21.2	0.04
ΔBNP (pg/ml)	−0.3 ± 7.8	5.4 ± 8.1	0.01

Values are expressed as mean ± SD. THP, pirarubicin.

is relatively low. However, it should be noted that EF and FS may not be sensitive parameters for monitoring cardiac injury, because they often remain normal until critical point in the face of cardiac compensation [30]. Tissue Doppler echocardiography (TDE) has became widely available. Since TDE gives a more precise estimation for diastolic dysfunction than the E/A ratio used in this study, it may be helpful in future studies [40].

Non-invasive techniques for identifying patients who are at high-risk of developing AC-induced cardiomyopathy are critically important. For this purpose, natriuretic peptides including BNP and N-terminal fragment of BNP pro-hormone (NT-pro-BNP), are currently used for detection of cardiac injury in both adults and children [41]. Until now, 4 studies have reported BNP levels in childhood cancer survivors who received AC therapy [28–31]. In 3 of these, elevated BNP levels were detected [28,30,31], although the values did not significantly correlate with cumulative AC doses. Our study showed no significantly different BNP levels in patients from controls, but BNP levels after exercise were significantly correlated to cumulative THP dose. A similar finding was reported by Pinarli et al. [30], in which they found high BNP levels after exercise by treadmill, but no correlation with cumulative AC dose. Since augmented response in plasma BNP levels to exercise has been reported in adult patients with left ventricular dysfunction or exercise-induced ischemia [42,43], the increased BNP levels and ΔBNP after exercise in our study may be associated with subclinical myocardial injury. The stability of BNP in blood samples should be considered when interpreting BNP values after exercise. McNairy at al. found that post-exercise BNP returned to baseline levels within 60 min for normal subjects [44]. On the other hand, NT-pro-BNP is characterized by its stability against protease and longer half-life in comparison with BNP. Thus, the measurement of NT-pro-BNP may provide additional evidence in the early detection of anthracycline-induced cardiotoxicity in childhood and adolescence.

Currently, the 6MWT is considered to represent the most suitable method to assess the exercise tolerance. This self-paced test is easy to perform, well tolerated, and highly acceptable to children [39,45]. In our study, all subjects finished the test without difficulty or premature stopping. Consequently, the 6MWT may be used both in assessment and follow up of functional capacity in childhood cancer survivors.

In conclusion, the present study suggested that THP-induced late cardiac dysfunction is rare. However, further investigation is warranted to clarify the pathopsysiological significance of elevated BNP levels after the exercise test in asymptomatic patients.

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Distinct Impact of Imatinib on Growth at Prepubertal and Pubertal Ages of Children with Chronic Myeloid Leukemia

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Objective To determine the extent of growth impairment resulting from imatinib treatment in children with chronic myeloid leukemia (CML).

Study design Clinical records of 48 chronic-phase CML children administered imatinib as the first-line therapy between 2001 and 2006 were analyzed retrospectively. Cumulative change in height was assessed using the height height-SDS and converted height data from age- and sex-adjusted Japanese norms.

Results A decrease in height-SDS was observed in 72.9% of children, with a median maximum reduction in height-SDS of 0.61 during imatinib treatment. Median follow-up time was 34 months (range, 10-88 months). Growth impairment was seen predominantly in children who started imatinib at a prepubertal age compared with those who started at pubertal age. Growth velocity tended to recuperate in prepubertal children with growth impairment, as they reached pubertal age, suggesting that imatinib had little impact on growth during puberty.

Conclusions Growth impairment was a major adverse effect of long-term imatinib treatment in children with CML. We report the distinct inhibitory effect of imatinib on growth in prepubertal and pubertal children with CML. We should be aware of growth deceleration in children, especially in young children given imatinib before puberty and subjected to prolonged exposure. *(J Pediatr 2011;159:676-81).*

Since the introduction of imatinib, the treatment of chronic myeloid leukemia (CML) has changed from cure by allogeneic stem cell transplantation to maintenance of the best achievable treatment response (hematologic, cytogenetic, and molecular responses). Various side effects, including nausea, vomiting, diarrhea, skin rash, edema, elevated liver enzyme values, and cytopenia, are known to be common during imatinib treatment, but generally are mild to moderate.[1] However, the long-term side effects of imatinib therapy remain unknown, and its effects on growth are a major concern when treating children. Growth deceleration has been reported in 3 children as well as in a cohort given imatinib.[2-5] The present study was conducted to evaluate the effect of imatinib on growth in children and adolescents with CML.

Methods

In Japan, imatinib was approved and became available for treatment of CML in December 2001. The Japanese Pediatric Leukemia/Lymphoma Study Group's CML Committee reviewed records of 99 Japanese children under age 18 years diagnosed with chronic-phase CML between 2001 and 2006. Among these children, 76 who received imatinib as first-line therapy were eligible for the study. Concurrent hydroxyurea administration was permitted. Exclusion criteria were as follows: (1) reached final height at the time of diagnosis (n = 3); (2) afflicted by a chronic disease (eg, schistorrhachis) or on any treatment that could affect growth (n = 4); and (3) a follow-up period of <10 months while receiving imatinib (n = 21). Forty-eight children (21 girls, 27 boys) met these criteria and were enrolled in the study. The study design was approved by the Keio University School of Medicine's Ethics Committee.

BSA	Body surface area
CML	Chronic myeloid leukemia
GH	Growth hormone
PDGF	Platelet-derived growth factor

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Height–Growth Evaluation

As part of the medical examination, height was measured by experienced medical workers at the start of imatinib treatment and at follow-up visits. Height data were converted to numbers with SDs using age- and sex-adjusted Japanese norms to give SDSs. Growth while on imatinib therapy was assessed using cumulative change in height-SDS (ΔSDS) from the start of imatinib treatment to the annual follow-up time points. Minimum height-ΔSDS was determined as the lowest value of annually calculated height-ΔSDS in each patient. Average dose of imatinib d_{ave} (mg/m^2) for an individual during the administration period (i) from 1 through n during l-year treatment was calculated using the following formulas:

$$\overline{d} = \frac{\sum_{i=1}^{n} d_i m_i}{\sum_{i=1}^{n} m_i}, \overline{BSA} = \frac{\sum_{j=1}^{l} BSAj}{\sum_{j=1}^{l} k_j}, \text{ and } d_{ave} = \frac{\overline{d}}{\overline{BSA}},$$

where d is the dose of imatinib, m is the number of days of imatinib administration, and BSA is body surface area (BSA). BSA in the jth year (BSA_j) was calculated from data obtained at the observation time point closest to the jth full-year point within 6 months. The value of k_j is 1 if BSA_j is available at the jth year and 0 otherwise. The data after reaching final height were censored for 2 patients. The final height was defined as the maximum height measured when height increase velocity slowed to <1 cm per year. In this study, age threshold equivalent to the onset of puberty was defined as 9 years for girls and 11 years for boys, as generally agreed upon by pediatricians.

Statistical Analyses

Statistical differences in height-SDS between 2 time points—at the commencement of imatinib treatment and at final follow up—within the cohort were assessed using the Wilcoxon signed-rank test. Statistical differences between the 2 subgroups classified according to minimum height-ΔSDS were assessed using the Mann-Whitney U test. The statistical differences among the 3 subgroups classified according to the average imatinib dose were evaluated using the Steel-Dwass test. The statistical differences among all annually calculated height-ΔSDS values during imatinib therapy in prepubertal and pubertal children at the commencement of imatinib treatment were assessed using the Tukey-Kramer honestly significant difference test.

Results

The median age at diagnosis was 9 years (range, 2-15 years). The median average imatinib dose was 287 mg/m^2 (range, 161-543 mg/m^2), and median follow-up was 34 months (range, 10-88 months). The overall median height of the 48 children was nearly normal at the start of imatinib treatment (median height-SDS, 0.01; range, −2.30 to 1.50), but was decreased significantly at the final measurement, with a median height-SDS of −0.85 (range, −2.80 to 1.30) ($P < .001$, Wilcoxon signed-rank test), indicating that imatinib adversely affected growth (**Figure 1**, A and B). Height <−2 SD at the last follow-up was observed in 6 children (12.5%), excluding 1 child whose height was <−2 SD at the start of imatinib treatment. A decrease in height-SDS of >0.5 SD was observed in 25 children (52.1%), including 16 (33.3%) with a decrease of >1 SD during imatinib treatment. The median minimum annually calculated height-ΔSDS during follow-up was −0.61 (range, −2.20 to 0.60) (**Figure 1**, C).

We next divided the study cohort according to their minimum height-ΔSDS into 2 subgroups: <−0.5 (n = 25) and ≥−0.5 (n = 23). Sex distribution, average imatinib dose, and proportion of patients with hydroxyurea administration were comparable between the 2 subgroups (**Table**). The greatest significant difference observed between the 2 subgroups was age at initiation of imatinib treatment. The proportion of prepubertal children was significantly higher in the minimum height-ΔSDS <−0.5 subgroup than in the ≥−0.5 subgroup. In contrast, the ≥−0.5 subgroup consisted mainly of children at pubertal age at the start of imatinib treatment.

To evaluate the relationship between administered imatinib dose and growth impairment, we divided the cohort according to the average administered dose for each individual and

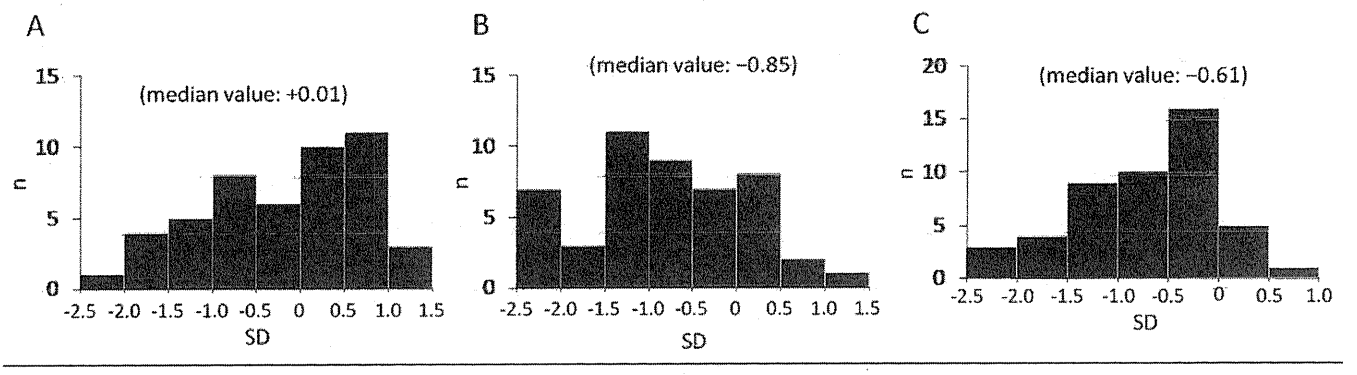

Figure 1. Change in height-SDS during imatinib treatment. Height-SDS is shown at **A,** the commencement of imatinib treatment and **B,** at the last follow-up. **C,** Minimum height-ΔSDS during imatinib treatment. The median value is indicated above each plot. n, number of patients.

Table. Patient characteristics

	Minimum height-ΔSDS		
	<−0.5 (n = 25)	≥−0.5 (n = 23)	*P* value
Age at the commencement of imatinib			
Median, years	7	12	<.001
Range, years	2-12	4-15	
Prepubertal age, n (%)*	23 (92.0)	4 (17.4)	<.001
Pubertal age, n (%)†	2 (8.0)	19 (82.6)	<.001
Male sex, n (%)	14 (56.0)	13 (56.5)	.9808
Duration of imatinib treatment, months, median (range)			
Prepubertal age*	42 (19-88)	14 (10-22)	.009
Pubertal age†	41 (21-60)	26 (10-61)	.406
Average imatinib dose, mg/m^2			
Median	293	282	.272
Range	161-543	197-376	
Hydroxyurea administration, n (%)	2 (8.0)	3 (13.0)	.577

*Prepubertal age: males, <11 years; females, <9 years.
†Pubertal age: males, ≥11 years; females, ≥9 years.

recommended pediatric doses for treating chronic-phase CML (260-340 mg/m^2)[6] into 3 subgroups: <260 mg/m^2 (n = 17), 260-340 mg/m^2 (n = 19), and >340 mg/m^2 (n = 12). The median minimum height-ΔSDS of these 3 subgroups was −0.6 (median dose, 222 mg/m^2), −0.48 (median dose, 293 mg/m^2), and −0.85 (median dose, 360 mg/m^2), respectively, indicating no significant difference among the 3 subgroups.

Representative growth charts of children at various ages at the start of imatinib treatment are shown in **Figure 2**. Growth impairment was particularly significant in children who were prepubertal at the start of imatinib treatment (**Figure 2**, A and B), and only mild growth impairment or no impairment was seen in most of the children who were pubertal at the start of imatinib treatment (**Figure 2**, C and D). However, the prepubertal children with growth impairment regained growth velocity as they reached pubertal age (**Figure 2**, E-H).

Mariani et al[2] reported a 9-year-old boy who demonstrated impaired growth shortly after the start of imatinib treatment but experienced catch-up growth with the onset of puberty. Thus, to evaluate whether children at pubertal age evade growth deceleration, we dichotomized the study cohort into 2 subgroups: children who started imatinib at prepubertal age (n = 27) and those who did so at pubertal age (n = 21). In the former group, height-ΔSDS began to decline during the first year of imatinib treatment, resulting in significant deceleration in growth. In the latter group, height-ΔSDS remained steady through imatinib treatment, suggesting that imatinib has little effect on growth in pubertal children (**Figure 3**).

Collectively, our data show a high frequency of growth impairment and >0.5 SD of cumulative decrease in height-SDS in children given imatinib for chronic-phase CML. This growth impairment was seen predominantly in young children who were started imatinib at prepubertal age.

Discussion

Imatinib is now a major option as the first-line therapy for childhood CML.[6-9] Thus, it is important for clinicians to be aware of its possible long-term effects. Imatinib inhibits several tyrosine kinases, including c-abl, c-kit, c-fms, and platelet-derived growth factor (PDGF) receptors.[7,10,11] Several studies in adults have suggested that inhibition of c-kit, c-fms, and PDGF receptors results in modulation of bone metabolism.[12-15] Inhibition of osteoclasts and osteoblasts may result in dysregulated bone remodeling.[11,15-17] Three recently published case reports indicated growth impairment as an adverse effect of long-term imatinib treatment in children.[2-4] In addition, a French group reported a significant decrease in height-SDS in 22 children, with a median difference of −0.37 (range, −1.09 to 0.14; $P < .0001$) during the first year of imatinib treatment.[5] Although the impact of imatinib on growth was noticeable in children in these previous studies, it has not yet been fully elucidated.

In our study of 48 children with chronic-phase CML, the severity of growth impairment was related to age at the start of imatinib treatment. Growth impairment was observed predominantly in children at prepubertal age compared with children at pubertal age. In children who started imatinib at prepubertal age, height-ΔSDS decreased during treatment, and in most cases, more than 2 years of continuous treatment was necessary to exhibit a reduction in height-SDS of >0.5 SD (**Figure 3**). Although 4 children who started imatinib at prepubertal age were included in the height-ΔSDS ≥−0.5 subgroup, these children were receiving imatinib for <2 years (**Table**), possibly indicating a high risk for developing severe growth impairment thereafter. We compared the distinct impact of long-term imatinib treatment on growth in prepubertal and pubertal children with CML.

Because the average imatinib dose varied among patients in our cohort, analysis was also performed according to the administered dose of imatinib. Although not significant, children exposed to imatinib doses >340 mg/m^2 showed a greater decrease in height-SDS compared with those exposed to lower doses, suggesting the need for further analysis to determine the correlation between imatinib dose and severity of growth impairment.

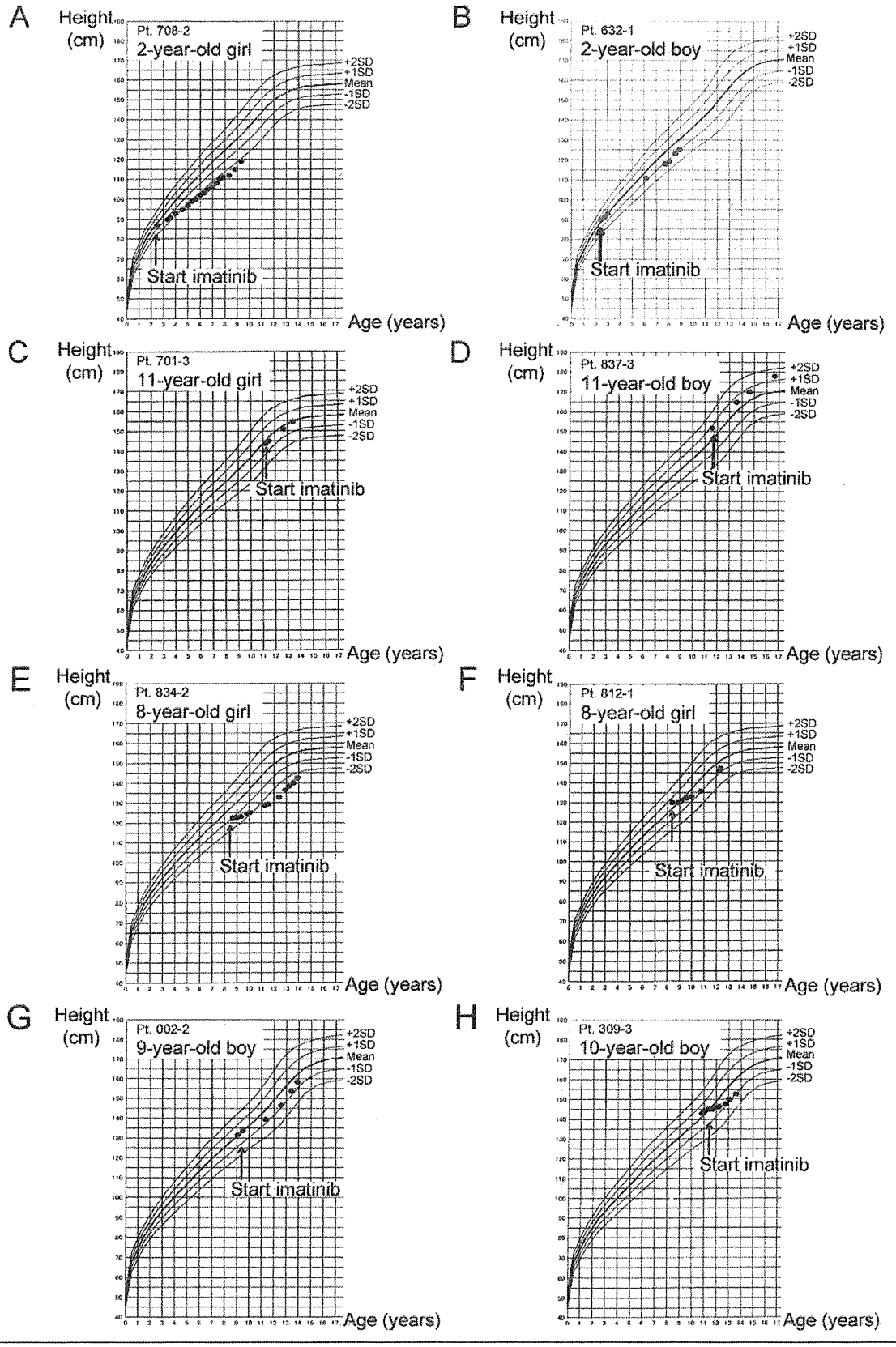

Figure 2. **A** and **B,** Representative height growth chart at the start of imatinib treatment of prepubertal children, and **C** and **D,** pubertal children. Growth impairment was observed in children at prepubertal age, but imatinib had little affect on growth in children at pubertal age. Impaired growth before puberty recovered as children reached pubertal age even during imatinib treatment. Catch-up growth was observed at **E** and **F,** approximately 11 years for girls, and **G** and **H,** 13 years for boys.

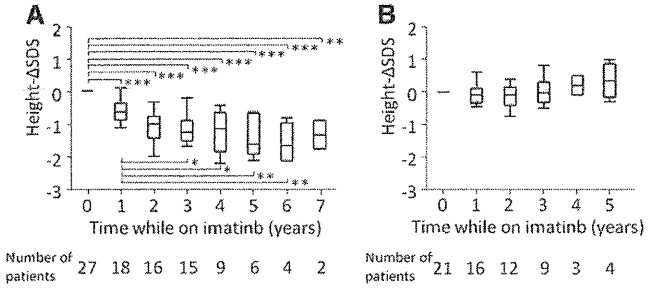

Figure 3. Height-ΔSDS during imatinib treatment of **A**, prepubertal (girls < 9 years, boys < 11 years) or **B**, pubertal children (girls ≥ 9 years, boys ≥ 11 years) in relation to age at the start of treatment. Annual height-ΔSDS is determined by subtracting height-SDS at each annual time point closest to each full-year point within ±6 months from the start of imatinib treatment. *$P < .05$; **$P < .01$; ***$P < .001$, Tukey-Kramer highly significant difference test.

Two previous reports demonstrated a recovery in growth velocity, one after discontinuation of imatinib treatment[3] and another at the onset of puberty even during imatinib treatment.[2] In our study, among 27 children who started imatinib at prepubertal age, 8 children were followed up over the pubertal age range; catch-up growth occurred in 4 children as they reached pubertal age, even during imatinib treatment (**Figure** 2, E-H). Human growth is described by the infancy-childhood-puberty growth model, and growth in puberty is dependent on the synergism between sex hormones and growth hormone (GH).[18] In these 4 children, noticeable catch-up growth was observed at approximately 11 years in girls (**Figure** 2, E and F) and 13 years in boys (**Figure** 2, G and H), consistent with the age at onset of the pubertal growth spurt.[18] These data support the hypothesis that imatinib has little effect on growth of children at pubertal age. Although more follow-up is needed to determine whether this catch-up is complete or incomplete, at least incomplete catch-up growth may be expected in the remaining 4 boys, who were only 13 years or younger at the last follow-up. Our study was performed based on generally agreed-upon prepubertal and pubertal ages, and more detailed studies are needed to determine the relationship between pubertal development and growth impairment.

Vandyke et al[19] recently reported that the rapid acceleration of growth plate closure resulting from the inhibition of PDGF-β receptor signaling by imatinib caused rapid acceleration of growth plate closure. However, bone age detected by wrist and hand X-rays showed no acceleration in other studies,[2,3] and the mechanism associated with the growth inhibitory effect of imatinib remains uncertain. A recent juvenile mouse model study indicated that long-term imatinib treatment impaired the length growth of tubular bone predominantly in prepubertal animals.[20] Consistent with this mouse model, growth impairment due to imatinib may be mild during the age period when height growth is dependent on sex hormones. Thus, imatinib may have a negative effect on GH or its functions. Indeed, Hobernicht et al[21] recently reported a case demonstrating iatrogenically induced GH deficiency due to tyrosine kinase inhibitor therapy for CML. However, performing a GH provocative test in all cohorts proved to be challenging, and moreover, the follow-up period was not of sufficient length for the majority of our cohort to allow determination of later effects on growth. To clarify the potential growth impairment mechanism of long-term imatinib treatment, further study with an extended follow-up period is needed to evaluate the growth recovery that likely would occur concomitantly with pubertal maturation. Because impaired bone remodeling and GH deficiency are caused by inhibition of tyrosine kinase, which is not specific to imatinib,[1,21] careful monitoring of growth velocity, as well as bone metabolic markers and serum insulin-like growth factor 1, is recommended for children treated with tyrosine kinase inhibitors. ■

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Original Article

Medical visits of childhood cancer survivors in Japan: A cross-sectional survey

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Abstract ***Background***: Although more children with cancer continue to be cured, these survivors experience various late effects. Details of the medical visit behaviors of childhood cancer survivors (CCS) in adulthood remain to be elucidated.

Methods: In order to examine medical visits in the past and future of CCS, we performed a cross-sectional survey with self-rating questionnaires on medical visits of CCS compared with control groups (their siblings and the general population).

Results: Questionnaires were completed by 185 CCS, 72 of their siblings and 1000 subjects from the general population and the results were analyzed. Mean ages at this survey and the duration after therapy completions of CCS were 23 and 12 years, respectively. We found that the previous treatment hospitals (where CCS were treated for their cancer) were the most commonly visited medical facilities for the CCS group (74% for female patients and 64% for male patients) and more than half of the CCS preferred to continue visiting the previous treatment hospital with enough satisfaction in Japan. The multivariate analysis showed that female sex and relapse were significantly associated with the past visits to the previous treatment hospital and that the CCS with brain tumors or bone/soft tissue sarcomas and CCS with any late effects tended to continue the relationships with the hospital. In addition female sex was also significantly associated with desired future visits to the previous treatment hospital. On the other hand, the married CCS tended to be disinclined to visit the hospital it in the future.

Conclusions: In order to optimize risk-based care and promote health for CCS after adulthood, we should discuss the medical transition with CCS and their parents.

Key words childhood cancer survivors, cross-sectional survey, health care, medical visit, transition.

As a result of advances in treatment, 70–80% of children who receive a diagnosis of cancer become long-term survivors. In Japan, the estimated number of childhood cancer survivors (CCS) is >50 000, or approximately 1 in 700 adults between 20 and 39 years. Although more children with cancer continue to be cured, these survivors experience various health problems or late effects from treatment, such as organ dysfunction, physical disabilities, reproductive problems, cognitive impairments, and an increased risk for developing secondary cancers.[1,2] Oeffinger *et al.*[3] reported that 62.3% of CCS exhibit at least one late effect and 27.5% exhibit two or more late effects. Our previous reports[4,5] also showed similar trends that late effects were observed in 50% of female CCS and 63% of male CCS. Because chronic conditions are common in CCS,[3] they need a continuous and comprehensive medical follow up after adulthood.

The details of the medical visit behaviors of CCS in adulthood remain to be elucidated. The Childhood Cancer Survivors Study (CCSS) demonstrated that less than 50% of CCS had a cancer-related visit and less than 20% of CCS had a visit at a cancer center after 15 years after the diagnosis.[6] Despite the low proportion of survivor-focused and risk-based care in North America, 87% of young adult CCS have a primary care or family physician in charge.[7] As the relationships between the attending pediatric oncologists or surgeons and CCS/their parents seem to be very intimate in Japan, their medical visit behaviors might be different from those in Western countries. We investigated the medical

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visit behaviors of young adult CCS and compared them with their siblings and the general population in Japan.

Methods

Study design

We performed a cross-sectional survey with self-rating questionnaires on medical visits of childhood cancer survivors compared with control groups (their siblings and the general population).[8] We simultaneously obtained medical data on the CCS from their attending pediatric oncologists or surgeons. The study was conducted from 1 August 2007 to 31 March 2009.

Participants and methods

The CCS and their siblings were recruited from the participating hospitals listed in the Appendix. The eligibility criteria for CCS were as follows: (i) the subjects were ≥16 years old at the time of survey; (ii) they were diagnosed as CCS at ≤18 years of age and >5 years had passed since the diagnosis of cancer; (iii) the subjects had continued in remission for >1 year without additional need for anticancer therapy; (iv) the subjects were informed about the diagnosis; and (v) informed consent was provided by CCS and their guardians. The criteria for subjects to be excluded from the survey were as follows: (i) the attending physicians believed that the survey would cause an undesirable effect on the CCS; (ii) the subjects had some underlying disease beside cancer, which affected their social outcome or quality of life; or (iii) the subjects were unable to answer the questionnaires by themselves. The general population was recruited by the Web-based research consulting company (Cross Marketing, Tokyo, Japan). The participants from the general population were selected by confirming that he or she neither had a childhood cancer experience nor a sibling with childhood cancer.

With the informed consent of the CCS or their siblings and their guardian, the attending pediatric oncologists or surgeons distributed questionnaires and asked the subjects to return them to the principal investigator (Y.I.) by mail anonymously within 1 month. On recruiting the general population group, the researcher contracted the role out to a cross-marketing organization that provides online research with Web-based methods using the same questionnaires for the research panel. The general population participants were matched with the CCS group in age, sex, living area, and job status.

Measurement of variables

Patient records were reviewed to obtain information about cancer-related variables, including diagnosis, birth year and month, age at diagnosis, age at therapy completion, treatment, and late effects of CCS. Late effects were defined as adverse events, which were grade 2 (symptomatic or needing some intervention) or higher using the Common Terminology Criteria for Adverse Events, Version 3 (CTCAEv3), originally developed by the National Cancer Institute (Japanese CTCAE v.3.0 by JCOG and JSCO, http://www.jcog.jp/). We classified the late effects into 14 categories: cardiovascular dysfunction, pulmonary dysfunction, endocrine dysfunction, short stature, kidney and bladder dysfunction, bone or muscle problems, skin problems or hair loss, neurocognitive impairment, gastrointestinal dysfunction, liver dysfunction, immunological dysfunction, secondary cancers, chronic infection, and others. Maintaining the confidentiality of medical information respects patients' privacy, so we used an encrypted number to send the data to the principal investigator.

We estimated the prevalence of outcomes among CCS and the control groups (their siblings and the general population). There are a total of 220 items in the questionnaire with three items for free writing. In this article we focused on the medical visiting items according to sex. It contains nine items: regular physical screening, visited clinics or hospitals during last 1 year, frequency of medical visits, reasons for medical visit, satisfaction with the visited clinics or hospitals, treatment summary, desired clinics or hospital to visit in future. Medical facilities were classified into nine categories: previous treatment hospital, hospital specialist, pediatric clinic, internal medicine clinic, long-term follow-up clinic, psychiatrist or psychologist, Oriental medicine, alternative medicine, and others. Previous treatment hospital was defined as the hospital where CCS were treated for their cancer during childhood. Hospital specialist was defined as the internal specialist in the same or different hospital as when the CSS received cancer treatment. The reasons for medical visit cited by them were classified into nine categories: annual routine check, childhood primary disease-related, common diseases (such as the common cold), complication-related, late-effects-associated, general health care, consultation for school or marriage, vaccination and others.

Ethical issues

The study was performed in accordance with the Declaration of Helsinki, and was approved by the ethics committee of the principal investigator's institution (Y. Ishida, Ehime University Graduate School of Medicine and St. Luke's International Hospital). The study was also approved by the local ethics committees of all the participating hospitals before initiation.

Statistical analysis

We performed χ^2-tests or Fisher's exact test (for any cells with expected counts <5) within categorical predictors, and the *t*-test or ANOVA for continuous variables. Adjusted odds ratios (OR) for target outcomes were estimated with the use of logistic regression analysis. To avoid multicollinearity, a pair-wise assessment of associations between predictors was examined. Data were analyzed with SPSS ver. 18.0 (IBM SPSS Japan, Tokyo, Japan).

Results

The demographic data of the participants are shown in Table 1. A total of 189 CCS (72% response rate) returned questionnaires but four CCS were excluded due to the following: two CCS had underlying disease besides cancer, which affected their quality of life; one questionnaire was written by the CCS's mother; and one CCS was 20 years of age at diagnosis. Also, we excluded two questionnaires from CCS siblings because two siblings were 14

Table 1 Demographic data of the participants

Group	Female			ANOVA or χ^2 (*P*-value)	Male			ANOVA or χ^2 (*P*-value)
	CCS (*n* = 108)	Siblings (*n* = 42)	General (*n* = 584)		CCS (*n* = 77)	Siblings (*n* = 30)	General (*n* = 416)	
Sex	58.4%	58.3%	58.4%	1.000	41.6%	42.7%	41.6%	1.000
Age at diagnosis	8.32 ± 4.8 (8.0)	10.1 ± 6.2 (9.0)	–	**<0.001**	8.53 ± 5.0 (8.0)	11.6 ± 4.1 (12.0)	–	**<0.001**
Age at survey	23.2 ± 4.9 (23)	25.6 ± 5.5 (24)	23.9 ± 5.4 (23)	**0.045***	23.1 ± 5.1 (22)	24.3 ± 4.6 (24)	23.8 ± 5.6 (23)	0.504
16–19 years of age	28 (26%)	3 (7%)	146 (25%)	0.285	19 (25%)	4 (13%)	102 (25%)	0.407
20–24 years of age	41 (38%)	20 (48%)	228 (39%)		34 (44%)	12 (40%)	187 (45%)	
25–29 years of age	25 (23%)	11 (26%)	134 (23%)		13 (17%)	10 (33%)	69 (17%)	
≥30 years of age	14 (13%)	8 (19%)	76 (13%)		11 (14%)	4 (13%)	58 (14%)	
Living area								
Kyusyu-Okinawa	33 (31%)	6 (14%)	173 (30%)	0.310	15 (20%)	2 (7%)	80 (19%)	0.514
Chu-Shikoku	24 (22%)	15 (36%)	131 (22%)		28 (36%)	9 (30%)	155 (37%)	
Kinki-Chubu	15 (14%)	9 (21%)	87 (15%)		10 (13%)	5 (17%)	52 (13%)	
Kantou-Koushin-Etsu	27 (25%)	11 (26%)	144 (25%)		22 (29%)	14 (47%)	118 (28%)	
Touhoku-Hokkaido	9 (8%)	1 (2%)	49 (8%)		2 (3%)	0	11 (3%)	
Work status								
Student	38 (35%)	13 (31%)	205 (35%)	0.140	29 (38%)	11 (37%)	173 (42%)	0.193
Part-time	15 (14%)	5 (12%)	58 (10%)		7 (9%)	4 (13%)	41 (10%)	
Full-time	36 (33%)	11 (26%)	230 (39%)		26 (34%)	15 (50%)	146 (35%)	
Others	19 (18%)	13 (31%)	91 (16%)		15 (20%)	0	56 (14%)	
Primary cancer								
Hematological	77 (71%)	NA	NA		51 (66%)	NA	NA	
Brain tumor	4 (4%)	NA	NA		6 (8%)	NA	NA	
Bone or soft tissue sarcoma	9 (8%)	NA	NA		9 (12%)	NA	NA	
Other solid tumor	18 (17%)	NA	NA		11 (14%)	NA	NA	
Treatment								
Multi-agents chemotherapy	105 (97%)	NA	NA		77 (100%)	NA	NA	
Radiation	68 (63%)	NA	NA		45 (58%)	NA	NA	
Stem cell transplantation	27 (25%)	NA	NA		19 (25%)	NA	NA	
Operation	34 (32%)	NA	NA		36 (47%)	NA	NA	
Recurrence	17 (16%)	NA	NA		16 (21%)	NA	NA	
Any late effects	54 (50%)	NA	NA		49 (64%)	NA	NA	

*Female CCS vs female siblings: $P = 0.035$ (Turkey) and 0.025 (Dunnett). Age was expressed as mean value ± SD (median value). CCS, childhood cancer survivors; NA, not available.

and 15 years of age at the time of survey, respectively. Mean ages at diagnosis were 8.3 years for female CCS and 8.5 years for male CCS. We conducted this survey at a mean age of 23.2 years for female and 23.1 years for male CSS. In regards to primary cancers, acute lymphoblastic leukemia comprised 44% of CCS, followed by acute myeloid leukemia/myelodysplastic syndrome, and lymphoma. Seventy percent of primary cancers were hematological. As for the treatment of the primary cancer, 98% of CCS received multi-agent chemotherapy, 61% radiation, 38% surgery, and 25% hematopoietic stem cell transplantation. Among CCS, one or more late effects were found in 56%, two or more late effects in 17% and three or more in 9%, respectively. Frequent late effects included endocrine dysfunction (21%), short stature (14%), bone/soft tissue damage (10%), liver dysfunction (9%), and skin disorder/hair loss (7%) (shown in the previous reports[4,5]).

Table 2 shows the clinical medical visits during the previous year. Both female and male CCS attended significantly more regular health screenings and regular medical visits than the control groups. Ninety-five percent of the CCS group visited some medical facilities during the previous year but only 29% of them knew about and had a treatment summary. One-third of CCS were not aware of the presence of the treatment summary. The previous treatment hospitals were the most commonly visited medical facilities for the CCS group (74% for female and 64% for male CCS). Internal medicine clinics (primary care physicians) were twice more common for the control groups compared to the CCS group. No difference was shown for frequency of medical visits among the three groups. Among the reasons given for visiting the hospital, all three groups had common problems, such as simple upper respiratory infection, vaccination and health care, however, only CCS had an annual routine health check, cancer-related, and complication- and late-effects-related visits.

Subjects who answered that they visited the outpatient medical facility during the previous year were questioned about their satisfaction with it. More CCS answered that they were satisfied with the present medical facilities than the control groups (Fig. 1). Among 126 CCS who visited the previous treatment hospital in the previous year, 107 (85%) CCS answered that it met their needs of a clinical visit, whereas 38 (70%) out of 54 who visited the internal medicine specialists, 25 (71%) out of 35 who visited the primary care physicians, and 19 (73%) out of 26 who visited the long-term follow-up clinic answered that it met their needs of a clinical visit. Figure 2 shows the most desired medical facility to visit in the future. Two-thirds of the CCS selected the previous treatment hospitals followed by the long-term follow-up clinic (26% of CCS). On the other hand, the internal medicine specialists followed by primary care physicians were significantly predominant in their siblings and the general population group.

We explored the factors associated with the CCS who visited the previous treatment hospital in the past and the future (Table 3). The univariate analysis showed that the CCS with any late effects, relapse and those unmarried visited the previous treatment hospital in the last year frequently and that the married CCS were disinclined to visit the previous treatment hospital in the future. The multivariate analysis showed that female sex and relapse were significantly associated with the past visits. Considering the high OR, the patients with brain tumors or bone/soft tissue sarcomas and CCS with any late effects tended to continue the relationships with the previous treatment hospital both in the past and the future. In addition, female sex was also significantly associated with the future visit to the previous treatment hospital, and the married CCS tended to be disinclined to visit the previous treatment hospital in the future. The CCS with longer duration after therapy completion had not visited the previous treatment hospital in the past (OR < 1.0) but wanted to do so in the future (OR > 1.0).

Discussion

We found that the previous treatment hospitals were the most commonly visited medical facilities for the CCS group and more than half of CCS preferred to continue to visit the previous treatment hospital with enough satisfaction even in young adulthood (23 ± 5, median 23 years of age). It is understandable that the CCS with brain tumors or bone/soft tissue sarcomas tended to continue the relationships with the previous treatment hospitals, because generally neurosurgeons and orthopedic surgeons are conducting clinical practices for all age patients in our country and CCS with brain tumors or bone/soft tissue sarcomas often need the care of specialists. We also found that female sex was associated with both past and future visits to the previous treatment hospital, which is compatible with the findings of Cox's report.[9]

Our results contrast with the results of CCSS.[6,10] Oeffinger *et al.*[6] reported that primary care physicians provide health care for most young adult CCS at a mean age of 26.8 years. They showed that 87% reported general medical contact, 71% a general physical examination, 42% a cancer-related visit, and 19%, a visit at a cancer center. But Hispanic CCS were more likely to report a cancer center visit (women: OR, 1.5; men: OR, 1.7).[11] Despite the high percentage of general medical contact, it is a problem that the majority of CCS do not receive recommended risk-based care.[7,10] In Western countries, risk-based health care for CCS has been promoted by nurse practitioners and/or primary care physicians (or general practitioners) recently.[12]

In our study, many CCS have received regular health examinations by the previous treatment hospitals during young adulthood as expected. This is a double-edged sword, because many CCS have continued to visit their previous treatment hospital well after completion of their treatment and through adulthood; many CCS often quit regular medical visits after their attending pediatrician's transfer or retirement. This is one of the main reasons of follow-up loss for CCS in Japan primarily because bonding between CCS and pediatricians might be strong, but also because special long-term follow-up clinics have not been widely established in Japan. To prevent this type of follow-up loss, CCS and their families should be fully informed of the importance of long-term follow up. After completion of treatment for the original cancer, we should provide the CCS and their parents with a

Table 2 Clinical medical visits during previous year

Gender	Female			χ^2 or Fisher's exact test (*P*-value)	Male			χ^2 or Fisher's exact test (*P*-value)
Group	CCS ($n = 107$)	Siblings ($n = 42$)	General ($n = 584$)		CCS ($n = 77$)	Siblings ($n = 30$)	General ($n = 416$)	
Regular health screening	82 (77%)	24 (57%)	302 (52%)	<0.0001	61 (79%)	20 (67%)	191 (46%)	<0.0001
Regular medical visit	77 (72%)	4 (10%)	59 (10%)	<0.0001	52 (68%)	2 (7%)	32 (8%)	<0.0001
Do you have a treatment summary?								
Know and have	29 (27%)	NA	NA	–	24 (31%)	NA	NA	–
Know but do not have	46 (43%)	NA	NA	–	26 (34%)	NA	NA	–
Do not know	32 (30%)	NA	NA	–	27 (35%)	NA	NA	–
Did you visit any medical facilities in the previous year?								
Yes	104 (97%)	36 (86%)	328 (56%)	<0.0001	71 (92%)	21 (70%)	152 (37%)	<0.0001
If yes, what kind of medical facility did you visit? (Count all)								
Previous treatment hospital	77 (74%)	2 (6%)	13 (4%)	<0.0001	49 (64%)	0	11 (7%)	<0.0001
Hospital specialist	27 (26%)	11 (31%)	99 (30%)	0.701	28 (36%)	8 (38%)	45 (30%)	0.308
Pediatric clinic	11 (11%)	0	11 (3%)	0.004	3 (4%)	0	4 (3%)	0.563
Internal medicine clinic	21 (20%)	15 (42%)	162 (49%)	0.0011	15 (21%)	8 (38%)	72 (47%)	<0.0001
Long-term follow-up clinic	17 (16%)	0	0	<0.0001	9 (13%)	0	0	<0.0001
Mental health clinic	1 (1%)	2 (6%)	36 (11%)	0.005	6 (9%)	0	11 (7%)	0.400
Oriental (*kanpo*) medicine	2 (2%)	0	11 (3%)	0.425	1 (1%)	1 (5%)	2 (1%)	0.499
Alternative medicine	17 (16%)	7 (19%)	34 (10%)	0.112	6 (9%)	2 (10%)	10 (7%)	0.817
Others	11 (11%)	7 (19%)	62 (19%)	0.134	5 (7%)	4 (19%)	24 (16%)	0.152
Frequency of clinic visits								
Once/year	15 (14%)	3 (8%)	41 (13%)	0.452	13 (18%)	7 (29%)	34 (22%)	0.421
2–3 times/year	31 (30%)	17 (47%)	126 (38%)		25 (35%)	8 (33%)	63 (41%)	
4–5 times/year	29 (28%)	9 (25%)	75 (23%)		14 (19%)	7 (29%)	31 (20%)	
6–10 times/year	13 (13%)	1 (3%)	27 (8%)		7 (10%)	1 (4%)	9 (6%)	
>10 times/year	16 (15%)	6 (17%)	59 (18%)		13 (18%)	1 (4%)	15 (10%)	
If you visited a medical facility last year, what was the purpose of your visit? (Count all)								
Annual routine check	75 (74%)	10 (29%)	84 (26%)	<0.0001	50 (71%)	7 (35%)	42 (28%)	<0.0001
Primary disease-related	9 (9%)	1 (3%)	2 (0.6%)	<0.0001	6 (9%)	0	2 (1%)	0.014
Common urgent care-related	39 (39%)	17 (50%)	164 (50%)	0.128	25 (36%)	10 (50%)	58 (38%)	0.508
Complication-related	7 (7%)	0	1 (0.3%)	<0.0001	5 (7%)	1 (5%)	0	0.005
Late-effects-associated	11 (11%)	0	0	<0.0001	3 (4%)	0	0	0.025
General health care	23 (22%)	7 (2%)	65 (20%)	0.859	17 (24%)	4 (20%)	26 (17%)	0.483
Consultation (school/marriage)	1 (1%)	2 (6%)	4 (1%)	0.093	1 (1%)	0	2 (1%)	0.871
Vaccination	34 (34%)	6 (18%)	85 (26%)	0.137	18 (26%)	4 (20%)	30 (20%)	0.593
Others	11 (11%)	5 (15%)	24 (7%)	0.233	5 (7%)	3 (15%)	9 (6%)	0.326

CCS, childhood cancer survivors; NA, not available.

Table 3 Clinical characteristics of childhood cancer survivors who visited or want to visit their previous treatment hospital

	Have visited the previous treatment hospital in last 1 year					Want to visit the previous treatment hospital in the future				
	Yes (n = 125)	No (n = 57)	χ^2 or Fisher's exact test (P-value)	Adjusted odds ratio (95% CI)	P-value	Yes (n = 94)	No (n = 54)	χ^2 or Fisher's exact test (P-value)	Adjusted odds ratio (95% CI)	P-value
Age at survey										
16–19 years of age	32	14	0.260			24	11	0.481		
20–24 years of age	55	20				37	24			
25–29 years of age	25	11				22	9			
≥30 years of age	13	12				11	10			
Sex: Female	77	29	0.174	**2.67 (1.27–5.62)**	**0.010**	60	27	0.100	**2.24 (1.05–4.78)**	**0.036**
Years after treatment completion										
0–9 years	44	11	0.065	Ref		29	18		Ref	
10–14 years	38	18		0.64 (0.24–1.73)	0.381	31	17		**1.41 (0.56–3.56)**	0.467
More than 14 years	43	28		0.66 (0.23–1.87)	0.435	34	19		**1.98 (0.68–5.71)**	0.208
Primary cancer										
Hematological cancer	85	41	0.053	Ref		69	39	0.643	Ref	
Brain tumor	9	1		**6.55 (0.62–69.1)**	0.118	6	2		**2.37 (0.40–13.9)**	0.339
Bone or soft tissue sarcoma	15	2		**3.99 (0.74–21.5)**	0.107	8	4		**2.13 (0.52–8.68)**	0.291
Other solid tumor	16	13		0.54 (0.20–1.45)	0.222	11	10		0.61 (0.21–1.79)	0.370
Any late effects	77	24	0.014	**2.05 (0.92–4.57)**	0.078	48	30	0.598	0.77 (0.34–1.76)	0.537
Relapse	29	4	0.009	**4.04 (1.17–14.0)**	**0.028**	18	9	0.707	1.38 (0.49–3.88)	0.541
Treatment										
Surgery	46	22	0.816			35	18	0.634		
Radiation	79	32	0.365			57	35	0.614		
Stem cell transplantation	34	12	0.376			26	12	0.466		
Social Factors										
Married	12	12	0.026	0.42 (0.15–1.20)	0.105	9	12	0.036	**0.34 (0.11–1.76)**	**0.054**
Student	57	19	0.091	1.81 (0.78–4.25)	0.170	40	20	0.413	1.52 (0.64–3.63)	0.341
Full-time job	43	19	0.922			35	17	0.530		
Annual income ≥ ¥2million	23	13	0.501			17	10	0.954		
Medical visits >3 times/year	64	25	0.308			44	34	0.077	0.56 (0.27–1.19)	0.561
Education > high school	77	39	0.375			66	32	0.175		
Treatment summary										
Know and have	37	16	0.774			34	13	0.223		
Know but do not have	47	25				34	24			
Do not know	41	17				25	19			

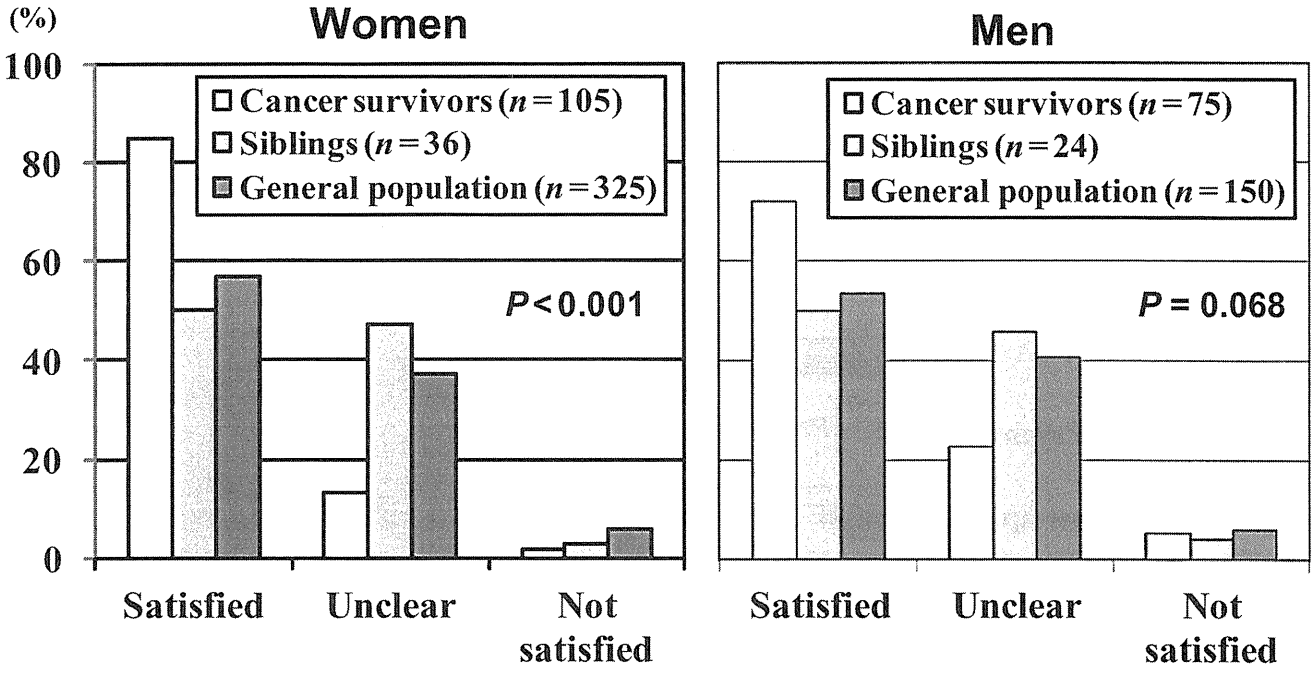

Fig. 1 Satisfaction for the outpatient medical facility. This question was limited to the subjects who went to the outpatient medical facility during the previous year. The childhood cancer survivors answered that they were more satisfied with the present outpatient medical facilities (85% for women and 71% for men) than their siblings (50% for both women and men) and the general population (56% for women and 53% for men).

treatment summary with suggestions on the type and timing of the follow-up evaluations to monitor the possible late effects.[13] In this survey, however, only 29% of them knew and had a treatment summary and there was no association between having the treatment summary and favor of visiting the previous treatment hospital. It doesn't suggest that CCS with information about the importance of long-term follow up want to visit the previous treatment hospital continuously.

The Erice statement[14] says, "when the survivor enters adulthood, he/she should be referred to an appropriate health care provider who coordinates long term care. If any specific problem arises that might be considered a possible late effect of treatments received during childhood, the survivor should be referred to an appropriate specialist." The fundamental purposes underlying health care transition from the pediatric to adult setting for young adult CCS are to optimize risk-based care and promote health for CCS after adulthood.[15,16] Care by pediatricians alone might be not enough to support the adult-oriented healthcare and prevention of lifestyle-related diseases in adulthood.[15] In our study, the preference to continue to visit the previous treatment hospital in future by more than half of the CCS might show that they don't understand the importance of adult-oriented health care.

On the other hand, most adult medical care providers, such as primary care physicians, in Japan are unfamiliar with CCS-specific care, and it is likely that some physicians in Japan are unaware of the existence of these types of high-risk populations.[17] Neither nurse practitioners nor general practitioners exist in Japan, whereas they play a central role in CCS care in Western countries. Increased dialog with not only CCS but also adult medical care providers, such as primary care physicians, on the importance of risk-based adult-oriented health care is needed continuously.

The limitations of our study were as follows: (i) the number of subjects was limited; (ii) patients with solid tumors were fewer than those with hematological cancers; (iii) a selection bias might be present when distributing the questionnaires because we didn't conduct random sampling; and (iv) we could not get incidence and time-to-event information because of the cross-sectional survey. But our report fills a niche in the published literature because there are few articles on medical visit behaviors of young adult CCS in Asian countries, including Japan.

Our study revealed that only just more than half of CCS prefer to continue to visit their previous treatment hospital with enough satisfaction in Japan. This key finding suggests that the medical transition to adult-oriented medical care is difficult and impractical now in Japan. To optimize risk-based care and promote health for CCS during adulthood, we should discuss the medical transition not only with CCS and their families but also with adult medical care providers, such as primary care physicians.

Acknowledgments

The institutions that provided patient data and recruited CCS to the survey are listed in the Appendix. We are grateful to Dr Gautam A. Deshpande (MD, a visiting researcher of St. Luke's International Hospital) for English editing of this manuscript.

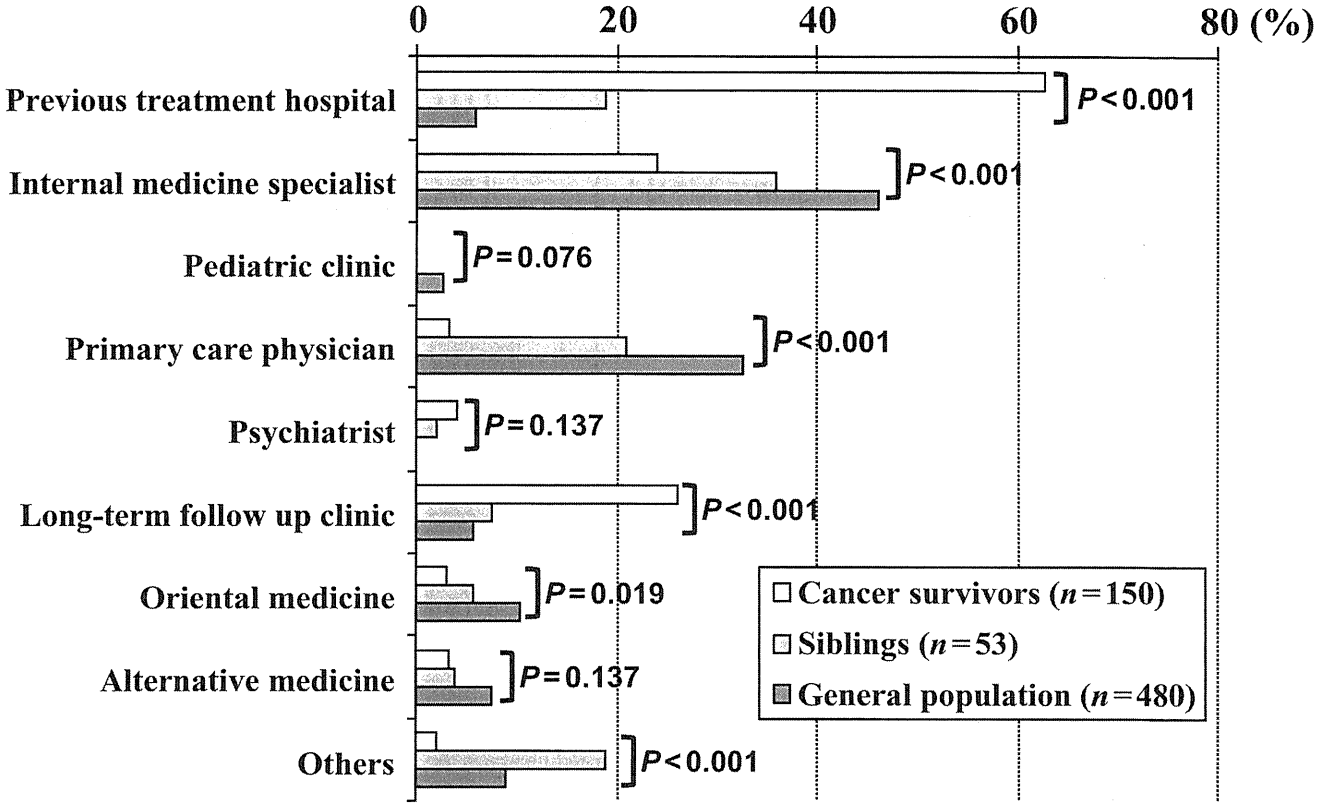

Fig. 2 The most desired medical facility to visit in the future. Sixty-three percent of the childhood cancer survivors answered that the previous treatment hospitals were the most desired medical facility, which was significantly higher than the proportion in the siblings and general population. On the other hand the most desired medical facility to visit in future for the siblings and the general population was the hospital internal specialists (36% and 46%) followed by the internal medicine clinics (21% and 33%).

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. The participant hospitals and investigators.

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ORIGINAL ARTICLE

Social outcomes and quality of life of childhood cancer survivors in Japan: a cross-sectional study on marriage, education, employment and health-related QOL (SF-36)

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Abstract Social outcomes and quality of life (QOL) of childhood cancer survivors (CCSs) remain unknown in Japan. We investigated these outcomes in young adult CCSs compared to those of their siblings in Japan, and analyzed the association between social outcome and SF-36 health survey subscale scores. Between 2007 and 2009, we performed a cross-sectional survey using self-rating questionnaires. We estimated social outcomes and health-related QOL by performing the SF-36 in each group: CCSs with or without stem cell transplantation (SCT)/radiotherapy (RT) and their siblings. Adjusted odds ratios for outcomes of interest were estimated using logistic regression analysis. Questionnaires from 185 CCSs and 72 CCS's siblings were analyzed. There were no differences in educational attainment or annual income. The SF-36 subscale scores of CCSs with SCT and RT were significantly lower than those of siblings in physical functioning (PF) ($p < 0.001$ and 0.003, respectively) and general health (GH) (both $p = 0.001$). Lower PF scores correlated with recurrence ($p = 0.041$) and late effects ($p = 0.010$), and poor GH scores with late effects ($p = 0.006$). The CCSs had made efforts to attain educational/vocational goals; however, a significant proportion of CCSs who had experienced late effects remain at increased risk of experiencing diminished QOL.

Keywords Childhood cancer survivors · Marriage · Education · Employment · Health-related QOL · SF-36

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1 Introduction

As a result of advances in treatment, 70–80% of children diagnosed with cancer become long-term survivors. In Japan, the estimated number of pediatric cancer survivors is upward of 50,000, or approximately one in 700 adults between the ages of 20 and 39 years. Although an increased number of children with cancer have been cured, many survivors experience various health problems or late effects as a result of their treatments [1, 2]. In addition to various physical problems in childhood cancer survivors (CCSs) [3], social outcomes vis-à-vis marriage, education and employment are apparently affected by these late effects, either directly or indirectly. An increasing number of studies have focused on the social outcomes of CCSs [4–12].

A Swedish population-based study [4] revealed that central nervous system (CNS) tumor survivors had poorer social outcomes compared to the general population, whereas outcomes for non-CNS cancer survivors were similar to those of the general population. On the other hand, the results of the Childhood Cancer Survivor Study (CCSS) suggest that CCSs generally have high school graduation rates similar to those in the general population, but they are slightly less likely to attend college; they are also more likely to be unemployed and not married as young adults [5]. Johannsdottir et al. [6] also outline important differences in social outcomes (i.e., employment and parenthood) between CCS and controls early in adult life.

The health-related quality of life (QOL) of CCSs has been studied extensively using the 36-item Short Form Health Survey (SF-36). Reulen et al. [13] demonstrated the validity and reliability of the SF-36 when used with CCSs, but they point out that ceiling effects should be recognized for researchers in using the SF-36 with CCSs. Maunsell et al. [14] show that QOL differences between CCSs and controls are small, and for the most part are probably not clinically important. In their study, survivors' scores on most subscales of the SF-36 were similar to those of controls, despite experiencing some difficulties in their daily activities [15].

Many reports including meta-analyses or systematic reviews of social outcomes [16] and QOL [17, 18] among CCSs have been published; however, the association between social outcomes and SF-36 scores remains to be elucidated [12, 19]. We have already reported that both stem cell transplantation (SCT) and radiotherapy (RT) are closely associated with the late effects of CCSs [20, 21] and that no significant differences are found between CCSs and siblings in terms of depression and anxiety, but CCSs have significantly more posttraumatic stress symptoms and greater posttraumatic growth [22]. In this article, we investigated the social outcomes and QOL of young adult CCSs with or without SCT/RT compared to those of their siblings in the same population, and analyzed the association between social outcomes and SF-36 subscale scores.

2 Patients and methods

2.1 Study design and participants

We performed a cross-sectional survey involving self-rating questionnaires vis-à-vis the social outcomes and QOL of CCSs, compared to those of the siblings [20, 23]. The study was conducted between 1 August 2007, and 31 March 2009. The subjects were divided into three groups: the CCS with or without SCT/RT, and siblings. The last group was considered as a control that matched with the CCSs with regard to genetic capabilities and environmental similarity. The CCS and their siblings were recruited from the participating hospitals listed in the supplemental appendix 1.

The eligibility criteria for CCSs and their siblings were as follows: (1) the subjects were 16 years old or older at the time of the survey, (2) CCSs had been diagnosed with cancer at 18 years of age or younger, (3) CCSs had been in continuous remission for more than 5 years since cancer diagnosis without any additional need for anticancer therapy, (4) they had been informed about their diagnoses, and (5) informed consent was provided by both CCSs/siblings and their guardians. If CCSs had two or more siblings, we selected the subject with the nearest age to the CCSs among the siblings. The exclusion criteria were as follows: (1) the attending physicians believed that the survey would cause an undesirable effect on CCSs, (2) the subjects had some underlying disease besides cancer that affected their social outcome or QOL, or (3) the subjects were unable to answer the questionnaires by themselves.

2.2 Methods

After obtaining appropriate informed consent, the CCSs were provided with an anonymous questionnaire by the attending pediatricians and asked to return it within post-one month. The patients' clinical records were reviewed to analyze cancer-related variables, including the diagnosis, birth year and month, age at diagnosis, age at therapy completion, time since diagnosis, treatment variables and the late effects of CCSs observed at the time of the survey. We used an encrypted numbering system for dispatching data to the principal investigator, to maintain the confidentiality of patient information. Late effects were defined as adverse events that were grade 2 (i.e., symptomatic or needing some intervention) or higher, according to the