A nationwide survey of late effects in survivors of juvenile myelomonocytic leukemia in Japan

Shuichi Ozono[1], Kazuo Sakashita[2], Nao Yoshida[2], Harumi Kakuda[2], Kenichiro Watanabe[2], Miho Maeda[2], Yasushi Ishida[2], Atsushi Manabe[2], Takashi Taga[2], and Hideki Muramatsu[2]

[1]Kurume Daigaku Igakubu Daigakuin Igaku Kenkyuka Shonikagaku Kyoshitsu
[2]Japan Children's Cancer Group (JCCG)

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Abstract

We conducted a cross-sectional study using a questionnaire to explore the late effects in survivors of juvenile myelomonocytic leukemia (JMML). The attending pediatric hematologist oncologists completed the questionnaires. All survivors (N=30) had undergone allogeneic hematopoietic stem cell transplantation. Approximately 83% survivors showed more than one late effect. The identified late effects included endocrine, dental, skin, ophthalmologic, musculoskeletal, pulmonary, neurocognitive, and cardiovascular dysfunction. The prevalence of short stature and cardiovascular and kidney dysfunction was significantly elevated among survivors aged [?]18 years. Therefore, a multidisciplinary follow-up system for survivors of JMML is crucial.

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Shuichi Ozono[1,11*], Kazuo Sakashita[2,11], Nao Yoshida[3,11], Harumi Kakuda[4,11], Kenichiro Watanabe[5,11], Miho Maeda[6,11], Yasushi Ishida[7,11], Atsushi Manabe[8,11], Takashi Taga[9,11], Hideki Muramatsu[10,11]

[1]: Kurume University School of Medicine, Department of Pediatrics and Child Health

[2]: Department of Hemato-Oncology, Nagano prefectural children's hospital

[3]: Department of Hematology and Oncology, Children's Medical Center, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan

[4]: Department of Hemato-Oncology, Chiba prefectural children's hospital

[5]: Department of Hemato-Oncology, Shizuoka prefectural children's hospital

[6]: Department of Pediatrics, Nippon Medical School

[7]: Department of Pediatrics, Ehime prefectural central hospital

[8]: Department of Pediatrics, Graduate School of Medicine, Hokkaido University

[9]: Department of Pediatrics, Shiga Medical College, School of Medicine

[10]: Department of Pediatrics, Nagoya University Graduate School of Medicine

[11]: Japan Children's Cancer Group (JCCG)

*Correspondence to**:**

Shuichi Ozono, MD, PhD, Department of Pediatrics, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan

Tel.: +81-942-31-7565, Fax: +81-942-38-1792, E-mail: ohzono_shyuuichi@kurume-u.ac.jp

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Abbreviations:	
CTCAE	Common Terminology Criteria for Adverse Events
CI	confidence interval
GVHD	graft-versus-host disease
HSCT	hematopoietic stem cell transplantation
JMML	juvenile myelomonocytic leukemia
OR	odds ratio
SCT	stem cell transplantation
TBI	total body irradiation

Abstract

We conducted a cross-sectional study using a questionnaire to explore the late effects in survivors of juvenile myelomonocytic leukemia (JMML). The attending pediatric hematologist oncologists completed the questionnaires. All survivors (N=30) had undergone allogeneic hematopoietic stem cell transplantation. Approximately 83% survivors showed more than one late effect. The identified late effects included endocrine, dental, skin, ophthalmologic, musculoskeletal, pulmonary, neurocognitive, and cardiovascular dysfunction. The prevalence of short stature and cardiovascular and kidney dysfunction was significantly elevated among survivors aged [?]18 years. Therefore, a multidisciplinary follow-up system for survivors of JMML is crucial.

Introduction

Juvenile myelomonocytic leukemia (JMML) is a rare myeloproliferative/myelodysplastic malignancy, typical in infancy and early childhood, characterized by fever, hepatosplenomegaly, and organ infiltration due to excessive production of monocytic and granulocytic lineage cells.[1,2] Approximately 90% patients with JMML show either somatic or germline mutations in their leukemia cells in the Ras pathway.[3] Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment for JMML, and a myeloablative preparative regimen based on a combination of busulfan with other cytotoxic agents is recommended.[2,4] The high prevalence of late effects among survivors treated with HSCT is a major issue for hematologists devoted to long-term follow-up because the median age for HSCT is 2–3 years.[5,6] However, limited studies have focused on data regarding the late effects in survivors of JMML who underwent HSCT, particularly in those treated with myeloablative regimens. We aimed to elucidate these effects using a nationwide, retrospective analysis of child and adolescent survivors who underwent HSCT.

Results

In this cross-sectional study, attending pediatric hemato-oncologists completed a questionnaire. Eligible survivors were recruited from a database of the myelodysplastic syndrome central review committee. All survivors—first diagnosed between July 1999 and December 2016—were alive at the time of the survey. The review board of each institution approved this study. The requirement for informed patient consent was

waived because of the nature of the study (chart review) and use of an opt-out method to collect study data from the survivors or their guardians.

We evaluated demographic (age, sex, and social background) and medical (treatment for JMML, conditioning regimen, and early morbidity) variables after HSCT (Table 1). The late effects assessed were short stature, underweight, and endocrine, cardiovascular, pulmonary, neurocognitive, gastrointestinal, nephrological, dental, musculoskeletal, ophthalmologic, and secondary neoplasm complications. Hematologist oncologists rated each late effect according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4. We evaluated the prevalence of each late effect before performing univariate analysis between the late effects and demographic and medical variables.

Among the 43 eligible survivors, 30 (70%) were included. More than 80% survivors had more than one late effect, and 10% had more than seven late effects. The median number of late effects (CTCAE grades 1–5) was 3.3. The chi-square test of independence was performed by comparing the number of late effects and age groups. Survivors aged [?]18 years showed a significantly high number of late effects (chi-square: 11.1; df=3; $p<0.05$).

A busulfan-based conditioning regimen was administered to 24 (80%) survivors. Total body irradiation (TBI)-included conditioning was conducted in four survivors for the first HSCT and in five survivors for the second SCT. Ten survivors underwent a second HSCT. Chronic graft-versus-host disease (GVHD) was observed in 33% survivors, and the most common category of GVHD was skin lesions. Regarding social background, 28 survivors were students, two were graduates, and two were part-time workers.

The prevalence of late effects is illustrated in the descending order in Supplemental Figure S1. The most common late effects were short stature and underweight, which were found in 53% survivors. The third most common late effect was dental problems such as permanent tooth loss. Spinocellular carcinoma of the skin was observed as a secondary neoplasm in one survivor 10 years after receiving TBI-conditioned HSCT. The correlation between the most recently measured height of survivors and time lapsed from diagnosis to survey is plotted in Supplemental Figure S2.

Table 2 showed the odds ratios and 95% confidence interval (CI) of the late effects and risk factors associated with age and conditioning regimen around HSCT. We found significantly greater pulmonary complications in survivors who received HSCT at an age of [?]2 years, with TBI as the conditioning regimen. Thyroid complications were observed in survivors who received multiple HSCTs and those aged [?]18 years at the time of the survey. Significantly high frequencies of heart and kidney complications were observed in survivors [?]18 years. Underweight and heart complications were observed in patients who received TBI as the conditioning regimen.

Discussion

The present study focused on the late effects of survivors of JMML. Strikingly, >80% survivors had at least one late effect, and 10% had more than seven late effects. Our data suggested that older survivors of JMML had more late effects. Allewelt[7]reported that 98% patients who underwent cord blood transplantation with a busulfan-based conditioning regimen experienced at least one late effect. A series of survivors transplanted with both TBI- and busulfan-conditioning regimens showed a high incidence of late effects.[8] These reports highlight the necessity of clinical care guidelines for long-term follow-up.

In this study, growth impairment was the most frequent late effect, as described in a series of reports on HSCT for younger children with leukemia; Tomizawa[9] revealed that 58.9% infantile acute lymphoblastic leukemia survivors, most of whom received HSCT in early infancy, showed short stature. We found a significant negative correlation between the height of survivors and time lapse from diagnosis to when this survey was conducted. Giorgiani[10] reported that survivors treated with busulfan-conditioned regimens grew normally. The third most frequent late effect was dental problems. HSCT in younger children is highly related to dental problems, including microdontia, enamel hypoplasia, and extensive caries. Although the prevalence was relatively low in this study, we confirmed results reported previously.[11,12]

In this long-term follow-up study, univariable analysis revealed that the prevalence of kidney, thyroid, and cardiovascular complications was significantly higher in survivors aged [?]18 years than in those aged <18 years. Künkele[13] reported that 17% acute leukemia survivors treated with HSCT showed renal toxicity.[13] While they found that TBI with high-dose chemotherapy could be a risk factor, we found no significant correlation between TBI and nephrotoxicity. This discrepancy may be due to the small number of patients who received TBI in this study. Although hypothyroidism is often reported after HSCT for various leukemias, it has rarely been reported in studies of JMML alone.[14]Thyroid complications were significantly related to the number of HSCTs, which in turn was related to the cumulative number of cytotoxic drugs or irradiation. We found that heart complications were significantly related to the time lapsed and TBI regimen. Future studies are needed to explore heart function over a longer period after HSCT.

Lastly, pulmonary complications were significantly related to a younger age at the time of HSCT- and TBI-regimen administration. Hoffmeister[15] reported that time lapse after HSCT, single-fraction TBI, diseases such as chronic myeloid leukemia/myelodysplastic syndrome/JMML, and chronic GVHD were significant risk factors for pulmonary complications. Therefore, the results of this study partly confirm those of previous research.

This study has several limitations. First, the number of participants was small. Second, the study design was cross-sectional, preventing us from drawing conclusions regarding causality. Third, in-depth medical surveys were not conducted for all aspects of late effects because of the retrospective hematologist oncologist-oriented survey.

In conclusion, this study revealed that growth, dental, endocrine, and skin complications were common in survivors of JMML. These findings suggest that risk-based late effect follow-up is needed for survivors of JMML to assess and treat potential outcomes.

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Legends

TABLE 1 Profile of the survivors

TABLE 2 : Odds ratio and 95% Confidence Interval (CI) regarding age of subjects and stem cell transplantation

*: $p<0.05$ according to the chi-square analysis of each category.

**: $p<0.01$ according to the chi-square analysis of each category.

SUPPLEMENTAL FIGURE S1 Prevalence of late effects

Abbreviation: SD, standard deviation

SUPPLEMENTAL FIGURE S2 Scatter diagram of height and time lapse from diagnosis.

Dotted lines indicate approximate straight lines.

Number of survivors	Number of survivors	30
Male vs. Female ratio	Male vs. Female ratio	20 :
		Mean
Age at diagnosis (years)	Age at diagnosis (years)	1.7
Age at 1st stem cell transplantation(years)	Age at 1st stem cell transplantation(years)	2.8
Period from diagnosis to the current survey(years)	Period from diagnosis to the current survey(years)	13.2
		N
Survivors who underwent 2nd SCT	Survivors who underwent 2nd SCT	10

Number of survivors	Number of survivors	30
Prevalence of chronic graft versus host disease(GVHD)	Prevalence of chronic graft versus host disease(GVHD)	10
	Contents of cGVHD: Skin[6]、Lung[3]、Liver[1]	Contents
Number of Late effects	Number of Late effects	N
None	None	5
1 3	1 3	13
4 6	4 6	9
7[?]	7[?]	3

Table 1. Profile of survivors

Risk Factor	Age at SCT (<2 years old)	Age at SCT (<2 years old)	Age at survey (>18years old)
Late effects	Odds ratio	95% CI	Odds ratio
Short stature	1.65	0.37 – 7.37	7.80
Underweight	1.65	0.37 – 7.37	3.00
Musculoskeletal problem	1.36	0.20 – 9.28	1.30
Pulmonary problem	1.60*	1.10 – 2.34	2.83
Neurocognitive problem	0.50	0.08 – 3.15	0.64
Cardiac Complication	2.77	0.26 – 29.05	9.50*
Nephrological Complication	0.80	0.11 – 5.82	80.0**
Thyroid Complication	0.16	0.01 -1.75	1.67**

Table 2: Odds ratio and 95% Confidence Interval (CI) regarding age of subjects and stem cell transplantation