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소아 고형 종양 치료 후 발생한 치료 연관 급성 골수성 백혈병

Therapy-related acute myeloid leukemia after the treatment of primary solid cancer in children

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2017년 1월

서울대학교 대학원
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홍경택의 석사학위논문을 인준함
2017년 1월

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Abstract

Therapy-related acute myeloid leukemia after the treatment of primary solid cancer in children

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Therapy-related acute myeloid leukemia (t-AML) or therapy-related myelodysplastic syndrome (t-MDS) has a dismal prognosis and is one of the second malignant neoplasms, which could be encountered by pediatric oncologist more frequently. We have reviewed our experience with pediatric t-AML/t-MDS during a 17-year period.

Between October 2000 and September 2016, 16 patients who had primary solid tumors were diagnosed with t-AML at the Seoul National University Children's Hospital. The primary solid tumors assessed included osteosarcoma (n=5), neuroblastoma (n=2), Wilms tumor (n=2), Ewing sarcoma (n=2), medulloblastoma (n=1), pineoblastoma (n=2), rhabdomyosarcoma (n=1), anaplastic ependymoma (n=1), and a malignant germ cell tumor (n=1). The median patient

age at the time of diagnosis of the primary solid tumors was 9.6 years (range, 0.1 - 15.4 years), and the median age at the time of diagnosis of t-AML was 14.0 years (range, 4.7 - 23.9 years). The crude estimated incidence rate of t-AML from pediatric primary solid cancer was 0.78%.

The median latency period from the end of the primary tumor treatment to the diagnosis of t-AML/t-MDS was 29 months (range, 6 - 130 months). Fifteen patients received induction chemotherapy after the diagnosis of t-AML. Among them, only 12 patients achieved complete remission (CR). Of the 12 patients who achieved CR, only 7 patients underwent hematopoietic stem cell transplantation (HSCT). The 3-year and 5-year overall survival (OS) rates were 33.7 ± 12.2% and 25.2 ± 11.7%, respectively, and the 3-year and 5-year event-free survival rates were 26.9 ± 11.5% and 20.2 ± 10.4%, respectively. The patients who underwent HSCT showed favorable 5-year OS rates (57.1 ± 18.7%), while the 5-year OS rates of those who did not undergo HSCT was 0%.

This study demonstrated that an achievement of CR and a subsequent HSCT can be the optimum solution for the treatment of t-AML, and this strategy showed an acceptable outcome. Screening patients who are susceptible to t-AML and preventing them from developing t-AML will be required in the future.

Keywords: therapy-related acute myeloid leukemia, therapy-related

myelodysplastic syndrome, pediatric, hematopoietic stem cell transplantation, solid tumor

Student Number: 2011-23785

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SMN	second malignant neoplasm
t-AML	therapy-related acute myeloid leukemia
t-MDS	therapy-related myelodysplastic syndrome
EFS	event-free survival
OS	overall survival
HSCT	hematopoietic stem cell transplantation
TRM	treatment-related mortality
i.v.	intravenously
CR	complete remission

Introduction

A second malignant neoplasm (SMN) is a second, separate cancer following the original primary neoplasm and it occurs after cancer treatment, such as cytotoxic chemotherapy or radiation therapy. The number of long-term survivors of cancer is expected to increase because of an improvement in the outcomes of childhood cancers in recent decades. However, this, in turn, could lead to an increase of patients with an SMN.

It is well known that childhood cancer survivors have a 3- to 10-fold increased risk of developing an SMN.[1-4] Among them, therapy-related acute myeloid leukemia (t-AML) has the shortest median latency time and a dismal outcome.[5,6] For this reason, pediatric oncologists are likely to encounter t-AML or therapy-related myelodysplastic syndrome (t-MDS) more often as an SMN compared with other secondary tumors.

Therapy-related AML and t-MDS show a dismal prognosis.[7] Although the outcome of t-AML/t-MDS in pediatric patients is better than that in adults[8], 5-year event-free survival (EFS) and overall survival (OS) rates of pediatric t-AML/t-MDS have been reported to be 14%-30%.[9-11] A study demonstrated a promising 5-year EFS (61.1%) among pediatric t-AML/t-MDS patients who underwent a hematopoietic stem cell transplantation (HSCT).[12] However, higher treatment-related mortality (TRM) rates[9] and disease progression rates[10] render it difficult to overcome the dismal late complication of

pediatric cancer survivors.

Certain chemotherapeutic agents are considered to be associated with t-AML/t-MDS. Topoisomerase II inhibitors are known to cause t-AML with *MLL* gene rearrangements,[8,13-16] whereas alkylating agents are more frequently associated with t-AML with aberrations in chromosomes 5 or 7.[8,17] As these two types of chemotherapeutic agents have frequently been used to treat pediatric patients with cancer, t-AML/t-MDS could always be a major concern.

Several studies in children have reported the outcomes of t-AML/t-MDS, in addition to the toxicities and the feasibility of the treatment[9-12]. However, the results are heterogeneous and lacking compared with those in adults. Therefore, we retrospectively analyzed pediatric patients with t-AML/t-MDS who were treated at the Seoul National University Children's Hospital during a 17-year period. To exclude the possible lineage switch of acute leukemia[18,19], only patients whose primary cancers were solid tumors were included in this study.

Materials and Methods

Patients

Between October 2000 and September 2016, 16 patients whose primary cancers were solid tumors were diagnosed with t-AML at the Seoul National University Children's Hospital. The cohort was identified by a retrospective medical record review. Search criteria included age <18 years at the time of diagnosis of the first solid cancer, and subsequent development of t-AML/t-MDS, which were defined as a new acute myeloid leukemia or myelodysplastic syndrome that developed after the treatment of primary cancer.

Data collection

Demographic characteristics, data concerning primary cancer, treatments (chemotherapy, radiotherapy, and HSCT), toxicity, and outcome data were collected for all patients by a review of their medical histories. Cumulative doses of chemotherapeutic agents were calculated, and the location and the dose of radiation therapy were determined. Chemotherapeutic agents were classified by their mechanisms of action, such as alkylating agents (e.g., cyclophosphamide, ifosfamide, melphalan, carboplatin, and cisplatin), topoisomerase 2 inhibitors (e.g., etoposide and doxorubicin), and antimetabolites (e.g., fluorouracil, methotrexate, and cytarabine). High group of alkylating agents was defined as patients who received a

cumulative dose of cyclophosphamide above 20g/m^2 or ifosfamide above 40g/m^2, or a high dose chemotherapy with autologous stem cell rescue using busulfan or melphalan. Moreover, a high group of topoisomerase II inhibitor was defined as patients who received a cumulative dose of etoposide above 3.2g/m^2 or adriamycin above 400mg/m^2.

The diagnosis of t-AML and t-MDS was made according to the WHO classification.[20] Cytogenetic analyses were conducted with trypsin-Giemsa banding technique and fluorescent in situ hybridization on bone marrow cells at the time of diagnosis. The latency period was defined as the time from the end of the primary tumor treatment to the diagnosis of t-AML/t-MDS.

Chemotherapy regimen

Induction chemotherapy was administered to 15 patients, while the remaining patient received palliative care due to disease progression. Among the 15 patients, 9 patients received an enocitabine-based regimen (enocitabine 200 mg/m^2/d once daily intravenously [i.v.] for 7-10 days plus idarubicin 10 mg/m^2/d once daily i.v. for 3 days), while 6 patients received a cytarabine-based regimen (3 patients: cytarabine 200mg/m^2/d for 7 days continuous infusion i.v. plus idarubicin 12 mg/m^2/d once daily i.v. for 3 days; 3 patients: high-dose cytarabine 3 g/m^2/dose twice daily for 4 days).

Of the 15 patients who received an induction chemotherapy, 7 underwent HSCT using a busulfan-fludarabine-based conditioning regimen. For all patients, the conditioning regimen was composed of busulfan and fludarabine (40 mg/m^2 once daily i.v. on days -8 to -3). For 5 patients, busulfan (120mg/m^2) was administered once daily as the first dose on day -8, and a targeted dose of busulfan was used according to the therapeutic drug monitoring results on days -7 to -5[21], while the remaining 2 patients received busulfan 30 mg/m^2 once daily for 5 days and 0.8mg/kg/dose four times a day for 4 days. For 6 patients, antithymoglobulin (Thymoglobulin; SangStat, Lyon, France and Genzyme, Cambridge, MA; 2.5mg/kg once daily i.v. on days -3 to -1) was administered and etoposide (20mg/kg once daily i.v. on days -4 to -2) was administered to 3 patients. A patient who did not receive antithymoglobulin was administered cyclophosphamide (14.5 mg/kg once daily i.v. on days -3, -2).

Statistical methods

Categorical variables and continuous variables were compared using the chi-square test and Student's *t*-test, respectively. OS and EFS were analyzed using the Kaplan-Meier method, and the difference in survival rates was determined using the log-rank test. *P* values $<$ 0.05 were considered statistically significant. Statistical analyses were performed using 'R' version 3.2.2 (www.r-project.org) and SPSS 20.0 (IBM-SPSS, Armonk, NY, USA).

Results

Characteristics of the patients and t-AML

Sixteen patients were diagnosed with t-AML between 2000 and 2016. Primary solid tumors in the patients included osteosarcoma (n=5), neuroblastoma (n=2), Wilms tumor (n=2), Ewing sarcoma (n=2), medulloblastoma (n=1), pineoblastoma (n=2), rhabdomyosarcoma (n=1), anaplastic ependymoma (n=1), and a malignant germ cell tumor (n=1). The median patient age at the time of diagnosis of the primary solid tumors was 9.6 years (range, 0.1 - 15.4 years) and 14.0 years for patients with t-AML (range, 4.7 - 23.9 years). The male-to-female ratio was 1:1. Among them, 3 patients had a family history of cancer. One patient had a sister with Wilms tumor, a mother with mucosa-associated lymphoid tissue lymphoma, and a grandfather with esophageal cancer. The remaining 2 patients had a mother with papillary thyroid cancer and a grandfather with gastric cancer, respectively.

Three patients initially presented with t-MDS. The blast counts at the time of diagnosis of t-MDS were 5.3%, 7.4%, and 4.8% in the 3 patients with t-MDS, respectively; within 1-2 months, these patients developed t-AML. Meanwhile, the remaining 13 patients initially presented with t-AML. The leukemic cells of 12 patients had abnormal cytogenetics, with a deletion of chromosome 5 or 7 as the

most frequently observed aberration. One patient, whose leukemic cells had normal cytogenetics, had internal tandem duplications of FMS-like tyrosine kinase 3. These data are listed in Table 1.

All patients previously received treatment with at least one alkylating agent. Cyclophosphamide was administered to 13 patients (median cumulative dose, 8400 mg/m^2 [range, 3000 - 39650 mg/m^2]), and ifosfamide to 8 patients (median cumulative dose, 29.3 g/m^2 [range, 19.9 - 60.0 g/m^2]). Twelve patients received etoposide (median cumulative dose, 3200 mg/m^2 [range, 1000 - 7650 mg/m^2]). The cumulative doses of all the chemotherapeutic agents are listed in Table 2. Radiation therapy was administered to 7 patients who had intracranial tumors (n=5), neuroblastoma (=1), or Wilms tumor (n=1). Craniospinal irradiation was administered to 4 patients, with a median dose of 16 Gy (range, 12.2 - 23.4 Gy), and local radiation therapy was administered to 4 patients.

The median latency period from the end of the primary tumor treatment to the diagnosis of t-AML/t-MDS was 29 months (range, 6 - 130 months).

To compare the characteristics of t-AML, latency period, and survival according to previous chemotherapy administered, patients were classified as high and low group of alkylating agents and topoisomerase II inhibitors as above mentioned. However, we could not find any differences of age, cytogenetics of t-AML, latency period ,and survival between each group due to small sample size. (Table 3)

Estimated incidence rate of t-AML

To estimate the incidence rate of t-AML of patients with primary solid cancer, we analyzed the patients with solid cancer of Seoul National University Children's Hospital. Between 2004 and 2015, over 12 years, a total of 1,677 patients with solid cancer were diagnosed. During the same period, 13 patients with t-AML developed. Although there could be a selection bias, considering that some of the patients with t-AML might have visited other hospital, the crude estimated incidence rate of t-AML from pediatric primary solid cancer was 0.78% (13/1,677).

Treatment of t-AML and the outcome

Fifteen patients received induction chemotherapy after a diagnosis of t-AML. Among them, only 12 patients achieved complete remission (CR). The median time from the diagnosis to the achievement of CR was 39 days (range, 16 - 88 days). One patient who did not receive induction chemotherapy and 3 patients who did not achieve CR died due to disease progression and combined complications.

Of the 12 patients who achieved CR, only 7 underwent HSCT (Table 4). Unfortunately, patients 12 and 14, who received double-unit cord blood transplantation, died of treatment-related complications (the causes were septic shock and cytomegalovirus infection, respectively).

Patients 6 and 13 relapsed after HSCT, and patient 6 died of disease progression. However, patient 13 received donor-lymphocyte infusion and is now disease-free. Patients 1 and 2 received only chemotherapy and relapsed during maintenance chemotherapy after 42.2 and 19.7 months post the first CR, respectively. Patients 8 and 15 died of early relapse and invasive aspergillosis, respectively. Patient 16 is on consolidation chemotherapy and plans to receive HSCT in 2 months.

Overall and event-free survival

The OS and EFS rates are displayed in Figure 1. The 3-year and 5-year OS rates were 33.7 ± 12.2% and 25.2 ± 11.7%, respectively, and the 3-year and 5-year EFS rates were 26.9 ± 11.5% and 20.2 ± 10.4%, respectively. The causes of death were disease progression (n=8), septic shock (n=1), cytomegalovirus infection (n=1), and invasive pulmonary aspergillosis (n=1). The patients who underwent HSCT showed a favorable 5-year OS rate (57.1 ± 18.7%), while the 5-year OS rate of those who did not undergo HSCT was 0%.

Comparison of t-AML and de novo AML

In order to better understand the difference of characteristics of leukemic cell and outcome, we constructed a control group of *de novo* AML, who were diagnosed at Seoul National University Children's Hospital between 2008 and 2015. The characteristics of t-AML and

de novo AML patients were presented in Table 5. The patients with t-AML showed lower age at diagnosis, higher incidence of initial MDS presentation, and more deletion of 5 or 7 chromosome, while patients with *de novo* AML more frequent balanced translocation, such as t(8;21)(q22;q22). Moreover, EFS rate and OS rate were markedly different between both groups (Figure 2).

Table 1. Characteristics of 16 patients with t-AML

Characteristics	
Median age at the diagnosis of primary cancer, years (range)	9.6 (0.1-15.4)
Median age at the diagnosis of t-AML, years (range)	14 (4.7-23.9)
Male, number of patients (%)	8 (50%)
Type of primary cancer, number of patients	
Osteosarcoma	5
Neuroblastoma	2
Wilms tumor	2
Ewing sarcoma	2
Medulloblastoma	1
Pineoblastoma	1
Rhabdomyosarcoma	1
Anaplastic ependymoma	1
Malignant germ cell tumor	1
Presentation of tAML/tMDS, number of patients	
tMDS -> tAML	3
tAML	13
Cytogenetics, number of patients	
Deletion 5 or 7	5
MLL rearrangement	3
normal	4
Complex	2
Isochromosome 17	1
Trisomy 11	1
FLT-ITD, number of patients	
Yes	1
No	8
Not available	7

t-AML indicates therapy-related acute myeloid leukemia; No., number; t-MDS, therapy-related myelodysplastic syndrome; FLT-ITD, internal tandem duplications of FMS-like tyrosine kinase 3

Table 2. Description of the Chemotherapy regimens and the radiation therapy for primary cancer

Pt. No.	Age at diag-nosis (year)	Sex	Presen-tation	Primary cancer	Chemotherapy for primary cancer (Cumulativedose,mg/m^2)				RT	Latency Period (Mo)
					CPM	IFO	VP16	Others		
1	15.9	M	t-AML	PBL	3,000			Cisp (600), Cytarabine (3,000), VCR (15)	Yes, CSI (12.2Gy)	47
2	17.2	M	t-AML	OSA		60,000	5,000	Cisp (250), ADR (240)	N/A	19
3	6.3	M	t-AML	OSA	7,200	25,950	1,000	Cisp (880), Carbo (560), ADR (170), MTX (24,000)	N/A	27
4	21.7	M	t-MDS → t-AML	MBL	3,000			Cisp (600), Cytarabine (3,000), VCR (15)	Yes, CSI (12.2Gy)	130
5	19.5	F	t-MDS → t-AML	NBL	39,650		6,200	Cisp (780), Carbo (5,400), ADR (540), VCR (24)	YES, Abdomen (22.5Gy)	8
6	15.2	F	t-AML	OSA		36,000		Cisp (720), ADR (252), MTX (168,000)	N/A	16
7	9.0	F	t-AML	Wilms	9,600		3,350	Carbo (3,600), Melphalan (210)	YES, Abdomen (15.0Gy)	6
8	6.8	M	t-AML	RMS	5,940	58,530	3,900	Carbo (4,745), VCR (36)	N/A	34
9	12.7	M	t-AML	ES	9,000		2,925	Cisp (270), Carbo (5920), VCR (62)	YES, CSI (23.4Gy), Tumor bed (30.6Gy)	75
10	7.5	F	t-AML	Wilms	20,600		7,650	Carbo (8,600), ADR (60), Melphalan (210)	N/A	47
11	11.1	F	t-AML	OSA		27,000		Cisp (720), ADR (525), MTX (84,000)	N/A	8
12	4.6	F	t-AML	AE	22,000	19,850	3,150	Cisp (340), Carbo (3160), VCR (27), Melphalan (178), Thiotepa (900)	N/A	31
13	14.3	F	t-AML	ES	8,400	24,000	1,450	ADR (90), VCR (10),	Yes, Vertex of	17

								Busulfan (480), Melphalan (140)	Scalp (36Gy)	
14	4.7	F	t-AML	NBL	15,600		1,510	Cisp (355), ADR (168), VCR (3)	Yes, Abdomen (12Gy)	39
15	17.8	M	t-AML	GCT	8,000		1,800	Carbo (1,800)	Yes, CSI (19.8Gy) Tumor bed (19.8Gy)	27
16	23.9	M	t-MDS → t-AML	OSA	3,000	31,500	3,250	Cisp (850), Carbo (5,850), ADR (470), Melphalan (210)	N/A	51

Pt. No. indicates patient number; CPM, cyclophosphamide; IFO, ifosfamide; VP16, etoposide; RT, radiation therapy; Mo, month; M, male; t-AML, therapy-related AML; PBL, pineoblastoma; Cisp, cisplatin; VCR, vincristine; CSI, craniospinal irradiation; Gy, gray; OSA, osteosarcoma; ADR, adriamycin; N/A, not applicable; Carbo, carboplatin; t-MDS, therapy-related myelodysplastic syndrome; MTX, methotrexate; MBL, medulloblastoma; F, female; NBL, neuroblastoma; Wilms, Wilms tumor; RMS, Rhabdomyosarcoma; ES, Ewing sarcoma; AE, anaplastic ependymoma; GCT, germ cell tumor.

Table 3. Comparison between high and low group of alkylating agents and topoisomerase II inhibitors

	Alkylating agents			Topoisomerase II inhibitors		
	high group (n=8)	low group (n=8)	*P* value	high group (n=8)	low group (n=8)	*P* value
Age at diagnosis, median years (range)	11.7 (4.6-23.9)	14.0 (4.7-21.7)	0.92	13.2 (6.8-23.9)	13.5 (4.6-21.7)	0.64
Initial MDS presentation, number of patients.	2 (25.0%)	1 (12.5%)	1.00	2 (25.0%)	1 (12.5%)	1.00
Cytogenetics, number of patients			0.97			0.13
del 5q/-5 or del 7q/-7	3 (37.5%)	2 (25.0%)		3 (37.5%)	2 (25.0%)	
MLL rearrangement	1 (12.5%)	2 (25.0%)		3 (37.5%)	0 (0.0%)	
Normal	2 (25.0%)	2 (25.0%)		2 (25.0%)	2 (25.0%)	
Complex	1 (12.5%)	1 (12.5%)		0 (0.0%)	2 (25.0%)	
Others	1 (12.5%)	1 (12.5%)		0 (0.0%)	2 (25.0%)	
Latency period, median months (range)	25 (6-51)	33 (8-130)	0.22	17.5 (6-51)	35 (17-130)	0.10
5yr EFS rate, % (SD)	14.3 (13.2)	25.0 (15.3)	0.56	28.6 (17.1)	12.5 (11.7)	0.37
5yr OS rate, % (SD)	28.6 (17.1)	25.0 (15.3)	0.99	28.6 (17.1)	18.8 (15.8)	0.56

MDS indicates myelodysplastic syndrome; No., number; EFS, event-free survival; OS, overall survival; SD, standard deviation.

Table 4. Characteristics and outcome of patients who underwent hematopoietic stem cell transplantation

Pt. No.	Achieve-ment of CR	Stage at HSCT	Conditioning regimen	ATG	Donor and Graft	Out-come
6	Yes	CR	BuFlu	Yes	MUD, PB	DOD
9	Yes	CR	BuFluVP	Yes	MUD, PB	Alive
10	Yes	CR	BuFluVP	Yes	MUD, BM	Alive
11	Yes	CR	BuFlu	Yes	MUD, PB	Alive
12	Yes	CR	BuFluVP	Yes	DUCB	TRM
13	Yes	CR	BuFluCy	No	Haploiden tical, PB	Alive
14	Yes	CR	BuFlu	Yes	DUCB	TRM

Pt. No. indicates patient number; CR, complete remission; HSCT, hematopoietic stem cell transplantation; ATG, anti-thymocyte globulin; Bu, busulfan; Flu, fludarabine; MUD, matched unrelated donor; PB, peripheral blood; DOD, died of disease; VP, etoposide; BM, bone marrow; DUCB, double unit cord blood; TRM, treatment related mortality; Cy, cyclophosphamide.

Table 5. Comparison of characteristics of t-AML and *de novo* AML

Characteristics	t-AML (n=16)	*de novo* AML (n=90)	*P* value
Median age at diagnosis, years (range)	10.9 (4.6-23.9)	13.5 (0.2-27.7)	0.037
Male, number of patients (%)	8 (50.0%)	44 (48.9%)	0.935
Initial MDS presentation, number of patients (%)	3 (18.8%)	3 (3.3%)	0.043
Cytogenetics, number of patients (%)			<0.001
del 5q/-5 or del 7q/-7	5 (31.2%)	2 (2.3%)	
MLL rearrangement	3 (18.8%)	16 (18.2%)	
normal	4 (25.0%)	17 (19.3%)	
complex	2 (12.5%)	14 (15.9%)	
balanced translocation	0 (0.0%)	32 (36.4%)	
others	2 (12.5%)	7 (8.0%)	
FLT-ITD, number of patients			0.29
Yes	1 (6.3%)	16 (17.8%)	
No	8 (50.5%)	65 (72.2%)	
Not available	7 (43.8%)	9 (10.0%)	

t-AML indicates therapy-related acute myeloid leukemia; MDS, myelodysplastic syndrome; FLT-ITD, internal tandem duplications of FMS-like tyrosine kinase 3

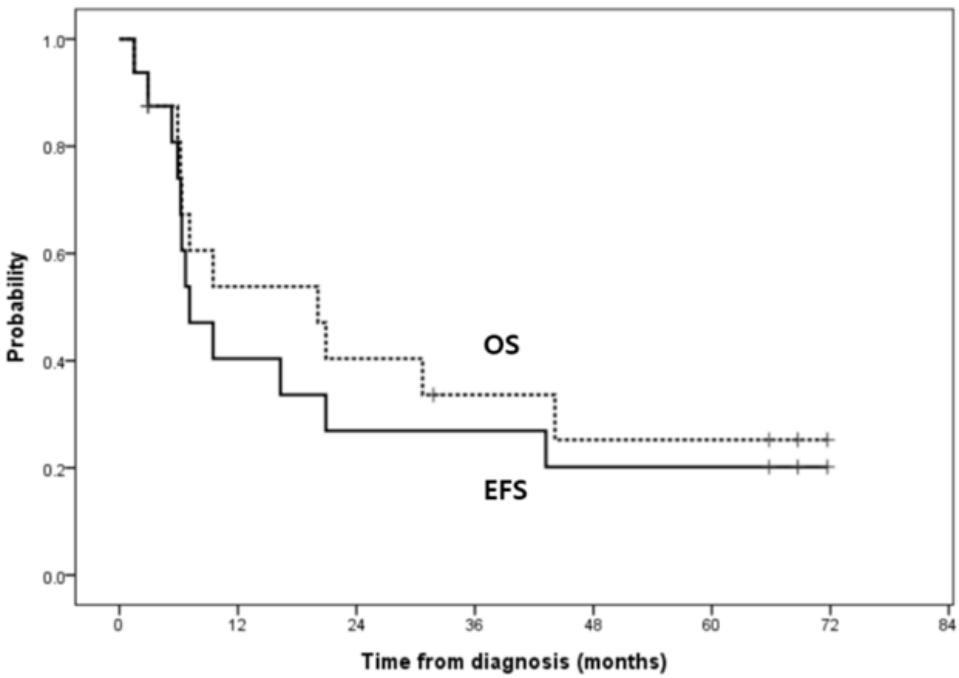

Figure 1. Overall survival (OS) and event-free survival (EFS) of all t-AML patients (N=16). Three-year and 5-year OS were 33.7 ± 12.2% and 25.2 ± 11.7%, respectively, and 3-year and 5-year EFS were 26.9 ± 11.5% and 20.2 ± 10.4%, respectively.

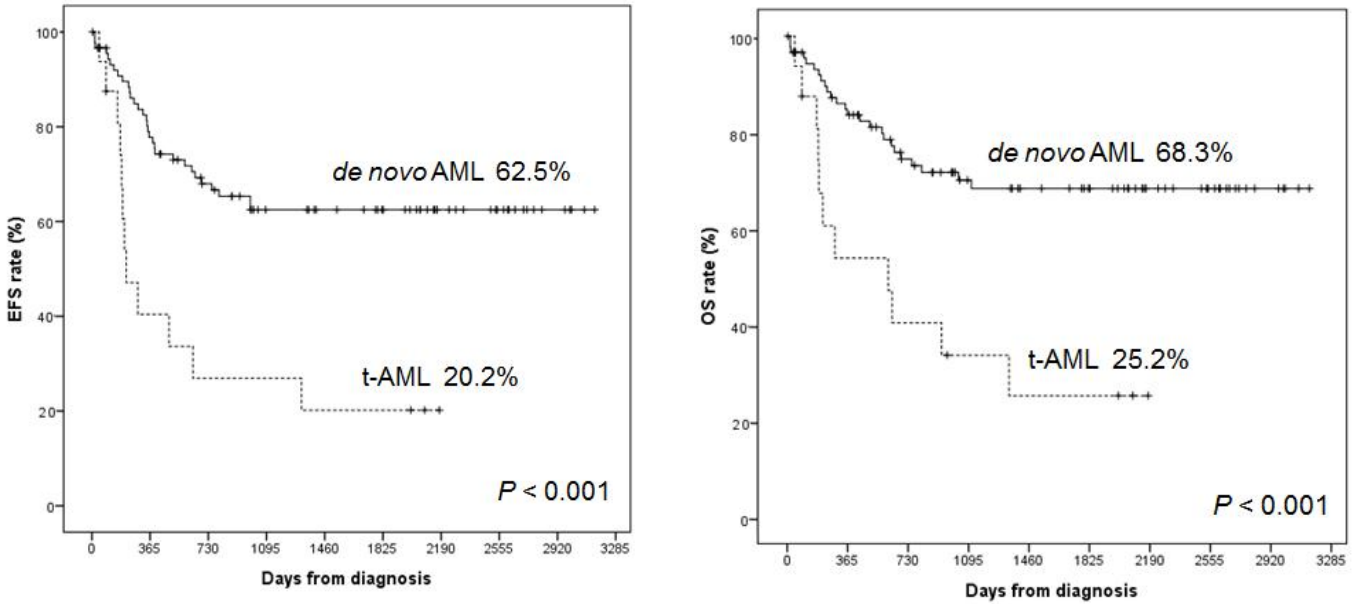

Figure 2. Comparison of event-free survival (EFS) and overall survival (OS) of t-AML patients (n=16) and *de novo* AML patients (n=90). There were significant differences in survival rates between both groups ($P<0.001$).

Discussion

Therapy-related AML/t-MDS is a dismal late complication after cytotoxic chemo- and radiotherapy in pediatric patients. In our analysis, the 3-year OS rate of all patients with t-AML was 33.7 ± 12.2%, and that of the patients who underwent HSCT was 57.1 ± 18.7%. These results are better than the results of earlier studies which reported 3-year OS rates of 15.4 ± 5.8%[9], 14.4 ± 8.0%[10], and 14.0%[11]. This could be explained because of improvements in leukemia outcomes over the last decade.

This study demonstrated that the achievement of CR and a subsequent HSCT could be the best solution for the treatment of t-AML, which is consistent with previous reports.[9-12] In our study, patients 1 and 2 achieved CR after induction chemotherapy; however, they refused to receive HSCT and relapsed subsequently at 42.2 and 19.7 months after the achievement of CR, respectively. This finding suggests that chemotherapy alone may not be sufficient for the treatment of t-AML, even though the initial response may be favorable.

A recent study showed 5-year OS rates of 61.1% in pediatric patients with t-AML/t-MDS using HSCT with busulfan, fludarabine, and melphalan as the conditioning regimen and T-cell depleted grafts.[12] Our conditioning regimen with targeted busulfan, fludarabine, and/or etoposide also resulted in a similar outcome. To overcome the

large obstacles of the higher probability of poor prognostic cytogenetic features of t-AML [7,10] and a higher tendency of inducing TRM owing to previous cytotoxic therapy[9], more sophisticated treatment and supportive care, such as a targeted busulfan to reduce organ toxicity[21] or T cell depleted grafts to reduce graft-versus-host disease[12], are required. Patients 12 and 14 died of infection and other treatment-related complications after HSCT. Moreover, patient 15 died of invasive pulmonary aspergillosis after consolidation chemotherapy. The results above suggest that vulnerability to cytotoxic drugs will always remain a concern, which also might be the cause of t-AML/t-MDS.

This study estimated the incidence rate of t-AML in pediatric primary solid cancer as 0.78%. This incidence rate could be meaningful because it was a result of the previous chemo and radiotherapy, not by the chance of lineage switch of leukemic cells.[18-19] However, because of a selection bias as a single center experience, further national or international epidemiologic study will be necessary.

Recently, in addition to cytogenetic abnormalities, several gene mutations that could serve a role in the pathogenesis of t-AML have been studied, such as point mutations in *TP53* or *AML1* genes, and mutations in downstream genes in the *RAS/BRAF* signal-transduction pathway.[22] This has revealed that t-AML is the result of an accumulation of numerous genetic mutations and

cytogenetic abnormalities.[23] This process is more complex in adults.[24] A higher incidence of *TP53* mutation in t-AML patients has been observed.[25] A recent study revealed that a *TP53* mutation found in t-AML cells was also detected at low frequencies at the time of diagnosis of the primary cancer, 3-6 years before the development of t-AML/t-MDS.[26] Therefore, a child who already possesses a few *TP53* mutated cells could have a higher possibility of developing t-AML or other SMNs. In future, these susceptible patients may be discovered prior to the use of cytotoxic therapy using advanced methods such as single cell genomics.[27]

In summary, we have detailed our experience with pediatric t-AML after the treatment of primary solid tumors. Although there are several obstacles to overcome, induction chemotherapy for AML and HSCT using targeted busulfan could be an acceptable option. However, the intensity of cytotoxic therapy has to be decided according to the medical condition of the patients because of their vulnerability to cytotoxic drugs. Furthermore, screening of susceptible patients and preventing them from developing t-AML will be necessary in the future.

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국문초록

치료 연관 급성 골수성 백혈병 또는 치료 연관 골수 이형성 증후군은 매우 불량한 예후를 가지는 병으로 알려져 있으며, 이차 암 중에서 비교적 조기에 발현하여 소아청소년과 의사가 더 흔히 접할 수 있는 질환이다.

2000년 10월부터 2016년 9월까지, 약 17년간 서울대학교 어린이 병원에서 고형암으로 치료 후, 치료 연관 급성 골수성 백혈병이 발생한 16명의 환자를 대상으로 연구를 진행하였다. 그들의 첫 번째 종양의 진단은 골육종 (5명), 신경모세포종 (2명), 윌름즈 종양 (2명), 유잉육종 (2명), 속질모세포종 (1명), 송과체모세포종 (1명), 역형성 뇌실막세포종 (1명), 횡문근육종 (1명), 악성 생식 세포종 (1명)이었다. 첫 번째 종양 진단 시의 중간 나이는 9.6세 (범위, 0.1-15.4세)였으며, 치료 연관성 급성 골수세포 백혈병 진단 시의 중간 나이는 14.0세 (범위, 4.7-23.9세)였다. 치료 연관 급성 골수성 백혈병의 예측 발생률은 0.78%로 확인되었다.

첫 번째 종양에 대한 치료 후 치료 연관 급성 골수성 백혈병 진단 시까지의 중간 잠복기는 29개월 (범위, 6-130개월)이었다. 15명의 환자가 관해 유도 항암치료를 시행 받았으며, 이 중 12명에서 완전 관해를 이루었고, 7명이 조혈모 세포 이식을 시행 받았다. 전체 환자의 3년 및 5년 생존률은 각각 33.7 ± 12.2%, 25.2 ± 11.7%이었으며, 3년 및 5년 무사건 생존률은 각각 26.9 ± 11.5%, 20.2 ± 10.4%이었다. 이 중 조혈모 세포 이식을 받은 환자들은 57.1 ± 18.7%의 5년 생존률을 보였으나, 그렇지 않은 군에서의 5년 생존률은 0%였다 (P=0.017).

이 연구를 통해 치료 연관 급성 골수성 백혈병의 가장 좋은 치료는 관

해 유도 후 빠른 조혈모 세포 이식술을 시행 받는 것임을 알 수 있었고, 이는 다른 연구의 성적과 비교하였을 때 비등한 결과를 보였다. 하지만, 이 환자들이 항암 치료에 의한 감염과 같은 합병증의 위험이 매우 높은 점을 고려하였을 때, 좀 더 각 환자의 상태에 대한 맞춤 치료가 필요할 것으로 생각된다. 또한, 이런 환자들을 미리 스크리닝하여 예방할 수 있는 방법에 대한 연구가 앞으로 더 진행되어야 할 것이다.

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주요어: 치료 연관 급성 골수성 백혈병, 치료 연관 골수 이형성증, 소아, 고형암, 조혈모 세포 이식술
학 번: 2011-23785