

Second Malignant Neoplasms in Childhood Cancer Survivors Treated in a Tertiary Paediatric Oncology Centre

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Abstract

Introduction: One of the most feared complications of childhood cancer treatment is second malignant neoplasms (SMNs). This study evaluates the incidence, risk factors and outcomes of SMNs in a tertiary paediatric oncology centre in Singapore. **Materials and Methods:** A retrospective review was conducted on patients diagnosed with childhood cancer under age 21 and treated at the National University Hospital, Singapore, from January 1990 to 15 April 2012. Case records of patients with SMNs were reviewed. **Results:** We identified 1124 cases of childhood cancers with a median follow-up of 3.49 (0 to 24.06) years. The most common primary malignancies were leukaemia (47.1%), central nervous system tumours (11.7%) and lymphoma (9.8%). Fifteen cases developed SMNs, most commonly acute myeloid leukaemia/myelodysplastic syndrome (n = 7). Median interval between the first and second malignancy was 3.41 (0.24 to 18.30) years. Overall 20-year cumulative incidence of SMNs was 5.3% (95% CI, 0.2% to 10.4%). The 15-year cumulative incidence of SMNs following acute lymphoblastic leukaemia was 4.4% (95% CI, 0% to 8.9%), significantly lower than the risk after osteosarcoma of 14.2% (95% CI, 0.7% to 27.7%) within 5 years ($P < 0.0005$). Overall 5-year survival for SMNs was lower than that of primary malignancies. **Conclusion:** This study identified factors explaining the epidemiology of SMNs described, and found topoisomerase II inhibitor use to be a likely risk factor in our cohort. Modifications have already been made to our existing therapeutic protocols in osteosarcoma treatment. We also recognised the importance of other risk management strategies, including regular long-term surveillance and early intervention for detected SMNs, to improve outcomes of high risk patients.

Ann Acad Med Singapore 2017;46:11-9

Key words: Late effects, Long-term cancer survivors, Topoisomerase II inhibitor

Introduction

Second malignant neoplasms (SMNs) have been recognised as a late complication of oncologic therapy since the 1970s,¹ as advancements in diagnosis and treatment of childhood cancer led to significant improvements in survival. SMNs are 3- to 7-fold as common in childhood cancer survivors as compared to the general population²⁻⁵ and represent a significant cause of morbidity and mortality in childhood cancer survivors, rising from 4% of mortalities at 5 to 10 years to 33% at 30 years after diagnosis.⁶ It is vital to identify and minimise patient exposure to the risk factors of SMN whilst not compromising cure rates.

Identified risk factors for SMNs involve both host- and treatment-related aspects, including younger age at diagnosis, underlying genetic predisposition, radiotherapy and chemotherapy.^{7,8} Secondary solid tumours have been associated with prior radiotherapy with a dose-dependent relationship, and are typically found within the radiation field following a latency of 10 years. On the other hand, the risk of haematological SMNs and myelodysplastic syndrome (MDS) is more strongly associated with chemotherapeutic agents. Specific characteristics have also been linked with certain chemotherapeutic agents, facilitating identification of risk factors in therapeutic protocols.⁹ Acute myeloid

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leukaemia (AML) related to alkylating agents and radiation are commonly of M1, M2, M6 and M7 phenotypes, and feature a relatively longer latency of 4 to 6 years with a myelodysplastic phase prior to leukaemic transformation. Deletions of all or part of chromosomes 5 and 7 are also typical. In contrast, secondary AML following treatment with topoisomerase II inhibitors (anthracyclines and epipodophyllotoxins) are often of M4 and M5 subtypes and occur within a short median latency of 24 to 33 months without a myelodysplastic phase. They are also associated with translocations to 11q23 (involving the mixed-lineage leukaemia [MLL] gene) and 21q22 (RUNX1). Other chromosomal abnormalities such as inv(16), t(15;17) and involvement of 11p15 (NUP98) have been linked with prior combination therapy with alkylating agents and topoisomerase II inhibitors. Regardless of aetiology, therapy-related leukaemias carry a poor prognosis.^{9,10} Understanding these associations enables the implementation of strategies such as modified regimens and surveillance protocols¹¹ to improve long-term outcomes for patients at risk.

While studies have been undertaken to characterise SMNs in regions such as Europe and North America, this is the first study to investigate SMNs within Singapore and Southeast Asia. We present findings of a retrospective review to evaluate the incidence, risk factors and outcomes of SMNs in long-term cancer survivors in a tertiary paediatric oncology centre in Singapore.

Materials and Methods

Patients and Methods

The Singapore Childhood Cancer Registry (SCCR) is a multi-institutional childhood cancer registry that studies the epidemiology of childhood cancers within our multiracial Asian population.¹² All childhood cancers were notified to the SCCR by 2 main institutions: KK Women's and Children's Hospital (KKH) and National University Hospital (NUH). These 2 institutions report more than 92% of childhood cancer cases in Singapore, with the remaining reported by private institutions. All cases captured are counterchecked with the Singapore Cancer Registry and the National Birth and Death Registry to ensure data accuracy.

All childhood cancer patients with primary malignancy or SMN, diagnosed under the age of 21 and treated at NUH between January 1990 and 15 April 2012, were included in this study. A list of these patients was generated from the SCCR, including data regarding their diagnoses and outcomes. Duration of follow-up was defined as the period from the date of diagnosis of primary neoplasm to the date of death or last known follow-up accurate up to the last review on 15 April 2014. Clinical records of all patients who had developed SMNs were individually reviewed.

Primary cancers and SMNs were classified according to the International Classification of Childhood Cancer (ICCC).¹³ SMN is defined as a histologically distinct cancer that develops after the first cancer. Non-melanoma skin cancers were also included. For patients who developed SMNs, pathological reports were reviewed for inclusion into the study and treatment-related data of the primary malignancy, relapses and conditioning for stem cell transplantations up to the event of SMNs were also collected.

Statistical Analysis

Cumulative incidence of SMN, overall survival and survival following specific neoplasms were calculated by Kaplan-Meier method with SPSS version 20.0 (SPSS Inc., USA). Ninety-five percent confidence interval (CI) was calculated from the standard error. Patients who were treated in other oncology centres for their primary cancer and referred to our centre for the management of SMNs were excluded from cumulative incidence and hazard ratio calculations but included in survival analysis. Hazard ratios were determined via a Cox regression model. Survival after SMN was defined as time from diagnosis of SMN to death from any cause, or until the last known follow-up.

Results

A total of 1124 patients were included in the study, including 4 who presented to the institution during their SMN. Median duration of follow-up was 3.49 (0 to 24.06) years and 857 patients were alive at the time of last data review. Of the 1124 patients, 670 (59.6%) patients were male and 454 (40.4%) female. Five-year overall survival was 73.8% (95% CI, 70.9 to 76.7%). Median age at diagnosis of primary malignancy was 5.43 (0 to 20.71) years. The most common primary malignancies were leukaemia (47.1%), central nervous system (CNS) tumours (11.7%) and lymphoma (9.8%); 31.4% were other malignancies. Table 1 shows the distribution of primary and second malignancies.

Second Malignant Neoplasms

Of the 1124 patients in the study, 15 developed SMNs, of whom 4 presented to our institution only during their SMN. It was made known to us that another patient had developed a benign second neoplasm (benign meningioma) 12.36 years after receiving chemotherapy and radiotherapy for medulloblastoma. In patients with SMN, the median age of diagnosis for primary and SMN were 6.24 (0.13 to 16.48) years and 14.56 (2.71 to 18.43) years, respectively, with a median interval period of 3.41 (0.24 to 18.30) years. The proportion of childhood cancer survivors that developed SMNs were 1.5% and 1.1% for males and

Table 1. Characteristics of Childhood Cancer Survivors (n = 1124)

Characteristics	No. of Patients (n, %)	Cases with SMN (n)
Vital status		
Alive	857 (76.2)	7
Dead	267 (23.8)	8
Gender		
Male	670 (59.6)	10
Female	454 (40.4)	5
Primary diagnosis*		
Leukaemia	529 (47.1)	7
CNS tumours	132 (11.7)	0
Lymphoma	110 (9.8)	3
Bone tumours	79 (7.0)	4
Neuroblastoma	65 (5.8)	0
Germ cell tumours	56 (5.0)	0
Soft tissue sarcomas	43 (3.8)	0
Retinoblastoma	39 (3.5)	0
Renal tumours	37 (3.3)	0
Hepatic tumours	26 (2.3)	0
Carcinomas	5 (0.4)	1
Others	3 (0.3)	0

CNS: Central nervous system; SMN: Second malignant neoplasms

*Diagnoses were classified according to International Classification of Childhood Cancer (ICCC)

females, respectively. The most common SMN was acute leukaemia (n = 11), followed by 2 cases of osteosarcoma and 1 each of atypical meningioma and peripheral T-cell lymphoma. Of the 11 cases of secondary leukaemia, 7 were AML/MDS, 2 were acute lymphoblastic leukaemia (ALL) and 2 were mixed phenotype acute leukaemia (MPAL). Excluding 4 patients who were referred to our centre during their SMN, the 10-year and 20-year cumulative incidence for development of SMN were 1.5% (95% CI, 0.3% to 2.7%) and 5.3% (95% CI, 0.2% to 10.4%), respectively (Fig. 1). The 15-year cumulative incidence of SMNs following ALL was 4.4% (95% CI, 0% to 8.9%), while the cumulative risk after primary osteosarcoma was significantly higher, reaching 14.2% (95% CI, 0.7% to 27.7%) within 5 years ($P < 0.0005$) (Fig. 2). The hazard ratio of developing SMN in patients with ALL compared to patients with other tumour types (excluding osteosarcoma) was 3.22 (95% CI, 0.625 to 16.61), whereas that of patients with osteosarcoma was 30.14 (95% CI, 5.48 to 165.71).

Table 2 summarises the clinical characteristics of patients who developed SMNs, including the type of primary and second malignancies, treatment received, chemotherapy

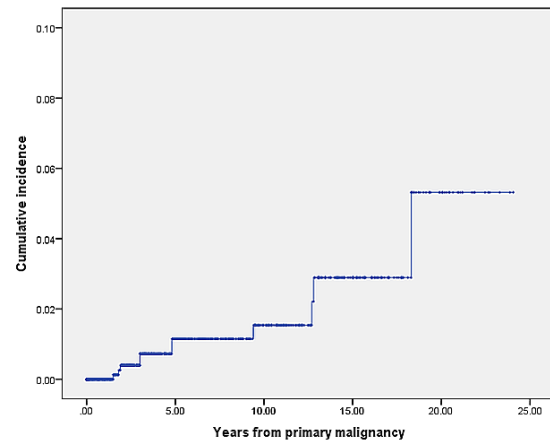


Fig. 1. Cumulative incidence of second malignant neoplasms in our centre.

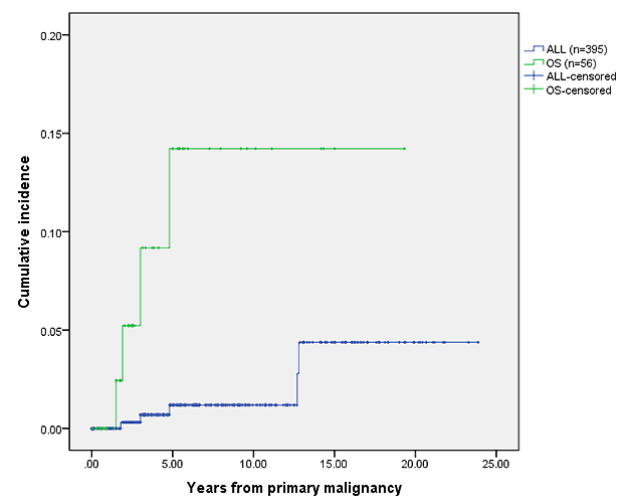


Fig. 2. Cumulative incidence of second malignant neoplasms in patients with acute lymphoblastic leukaemia and osteosarcoma.

ALL: Acute lymphoblastic leukaemia; OS: Osteosarcoma

regimen, latency and outcomes. Two patients had a positive family history of cancer in their second-degree relative.

In view of late effects associated with radiation in childhood, only a limited number of patients in our programme received radiation as part of primary therapy. Of the patients with SMNs, 2 patients were exposed to radiotherapy and both had ALL—1 received cranial radiation in combination with chemotherapy for ALL relapse (CNS and bone marrow), while the other underwent total body irradiation as part of the preparative regimen for allogeneic stem cell transplant (SCT). Both patients subsequently developed haematological malignancies (AML and MPAL, respectively). Another patient with mixed gonadal

Table 2. Clinical Characteristics of Patients with SMN

No.	Gender	Primary Neoplasm	Age at Diagnosis	Treatment of Primary Neoplasm*	Chemotherapy	SMN	Age at Diagnosis	Latency	Treatment of Second Neoplasm	Outcome
1	M	ALL	6.5	Chemotherapy (MASPORE ALL 2010 HR), 2 x Allogenic SCT (with TBI)	6-MP, 6-TG, ATG, Ara-C, CPM, Clo, Dasatinib, DNR, Flu, Imatinib, L-aspar, MTX, Pred, VCR, VP-16	MPAL	9.5	3.0	Chemotherapy + adoptive cell therapy	DOD
2	F	ALL	4.5	Chemotherapy (NUH 1996)	6-MP, 6-TG, Ara-C, CPM, Dexamethasone, DNR, L-aspar, MTX, Pred, VCR, VM-26	MPAL	17.2	12.7	Chemotherapy + allogenic SCT (with TBI)	A-NED
3†	M	ALL	3.5	Chemotherapy (NUH 1996)	6-MP, 6-TG, Ara-C, CPM, Dexamethasone, DNR, L-aspar, MTX, Pred, VCR, VM-26	AML	16.3	12.8	Chemotherapy + allogenic SCT	DOTC
4	M	ALL	7.5	Chemotherapy (MASPORE ALL 2002 SR & 2003 HR, FLAG) + RT	6-MP, 6-TG, Ara-C, CPM, Dexamethasone, DNR, DXR, Flu, L-aspar, MTX, Pred, VCR	AML	12.3	4.8	Allogenic SCT (with TBI)	AWD
5	M	ALL	6.2	Chemotherapy (MASPORE ALL 2002/2010 IR)	6-MP, 6-TG, Ara-C, CPM, Dexamethasone, DXR, L-aspar, MTX, Pred, VCR	NHL	8.1	1.8	Chemotherapy	DOD
6‡	F	Disseminated LCH	0.4	Chemotherapy (LCH II, LCH-S-98)	2-CdA, 6-MP, CsA, MTX, Pred, VBL, VP-16	ALL	18.4	18.0	Chemotherapy	DOTC
7†	M	Burkitt's lymphoma	5.1	Chemotherapy (Lyon 903)	Ara-C, CPM, DXR, MTX, Pred, VCR, VP-16	Atypical meningioma	14.5	9.4	Surgery	A-NED
8	M	Osteosarcoma	12.7	Chemotherapy (OS protocol with MTP) + surgery	CDDP, DXR, MTP, MTX	MDS	14.6	1.9	Supportive care	AWD
9	M	Osteosarcoma	9.1	Chemotherapy (NUH protocol A) + surgery	CDDP, DXR, IFO, MTX, VP-16	AML	12.1	3.0	Chemotherapy + allogenic SCT (with TBI) + adoptive cell therapy	AWD
10	M	Osteosarcoma	12.7	Chemotherapy (NUH protocol A) + surgery	CDDP, DXR, IFO, MTX, VP-16	AML	17.5	4.8	Chemotherapy	DOD
11†	F	Osteosarcoma	15.4	Chemotherapy (NUH protocol B) + surgery	CDDP, DXR, IFO, MTX, VP-16	AML	16.9	1.5	Chemotherapy + allogenic SCT (with TBI)	DOD

2-CdA: Cladribine; 6-MP: Mercaptopurine; 6-TG: Thioguanine; ABVD: Adriamycin, bleomycin, vinblastine and dacarbazine; ALL: Acute lymphoblastic leukaemia; AML: Acute myeloblastic leukaemia; A-NED: Alive with no evidence of disease; Ara-C: Cytarabine; ATG: Anti-thymocyte globulin; AWD: Alive with disease; Bleo: Bleomycin; CCNU: Lomustine; Clo: Clofarabine; CPM: Cyclophosphamide; CsA: Cyclosporine A; Dexamethasone; DNR: Daunorubicin; DOD: Died of disease; DOTC: Died of treatment complication; DXR: Doxorubicin; F: Female; FLAG: Fludarabine, cytarabine and granulocyte colony-stimulating factor; Flu: Fludarabine; HR: High risk; IFO: Ifosfamide; IR: Intermediate risk; L-aspar: L-asparaginase; LCH: Langerhans cell histiocytosis; M: Male; MASPORE ALL: Singapore-Malaysia acute lymphoblastic leukaemia treatment protocol; MPAL: Mixed phenotype acute leukaemia; MRC: Medical Research Council; MTP: Muramyl tripeptide; MTX: Methotrexate; NHL: Non-Hodgkin lymphoma; NUH: National University Hospital; OS: Osteosarcoma; Pred: Prednisolone; RT: Radiotherapy; SCT: Stem cell transplant; SMN: second malignant neoplasm; SR: Standard risk; TBI: Total body irradiation; VBL: Vinblastine; VCR: Vincristine; VM-26: Teniposide; VP-16: Etoposide

*Chemotherapeutic protocols are reflected in brackets.

†Patients with family history of cancer in 2nd degree relatives.

‡Patients with a third malignant neoplasm (not reflected in table).

§Patient was treated at multiple centres for her primary neoplasm.

¶Patients who presented during their SMN.

Table 2. Clinical Characteristics of Patients with SMN (Con't)

No.	Gender	Primary Neoplasm	Age at Diagnosis	Treatment of Primary Neoplasm*	Chemotherapy	SMN	Age at Diagnosis	Latency	Treatment of Second Neoplasm	Outcome
12 [‡]	F	Thyroid carcinoma	16.5	Surgery + radioiodine	-	Osteosarcoma	16.7	0.2	Chemotherapy + surgery	DOD
13	F	ALL	5.9	Chemotherapy	6-MP, 6-TG, Ara-C, CPM, Dexamethasone, DXR, L-asparaginase, MTX, Pred, VCR	AML	9.3	3.4	Chemotherapy + allogeneic SCT	A-NED
14	M	AML	0.8	Chemotherapy (MRC 15)	Ara-C, DNR, Flu, Mitoxantrone, VP-16	ALL	2.7	1.9	Chemotherapy	DOTC
15	M	Hodgkin's lymphoma	3.0	Chemotherapy (ABVD)	Bleo, Dacarbazine, DXR, VBL	Osteosarcoma	15.4	12.4	Chemotherapy + surgery	A-NED

2-Cda: Cladribine; 6-MP: Mercaptopurine; 6-TG: Thioguanine; ABVD: Adriamycin, bleomycin, vinblastine and dacarbazine; ALL: Acute lymphoblastic leukaemia; AML: Acute myeloblastic leukaemia; A-NED: Alive with no evidence of disease; Ara-C: Cytarabine; ATG: Anti-thymocyte globulin; AWD: Alive with disease; Bleo: Bleomycin; CCNU: Lomustine; Clo: Clofarabine; CPM: Cyclophosphamide; Csa: Cyclosporine A; Dexamethasone; DNR: Daunorubicin; DOD: Died of disease; DOTC: Died of disease; DXR: Doxorubicin; F: Female; FLAG: Fludarabine, cytarabine and granulocyte colony-stimulating factor; Flu: Fludarabine; HR: High risk; IFO: Ifosfamide; IR: Intermediate risk; L-asparaginase; LCH: Langerhans cell histiocytosis; M: Male; MASPORE ALL: Singapore-Malaysia acute lymphoblastic leukaemia treatment protocol; MPAL: Mixed phenotype acute leukaemia; MRC: Medical Research Council; MTP: Muramyl tripeptide; MTX: Methotrexate; NHL: Non-Hodgkin lymphoma; NUH: National University Hospital; OS: Osteosarcoma; Pred: Prednisolone; RT: Radiotherapy; SCT: Stem cell transplant; SMN: second malignant neoplasm; SR: Standard risk; TBI: Total body irradiation; VBL: Vinblastine; VCR: Vincristine; VM-26: Teniposide; VP-16: Etoposide

*Chemotherapeutic protocols are reflected in brackets.

[†]Patients with family history of cancer in 2nd degree relatives.

[‡]Patients with a third malignant neoplasm (not reflected in table).

[§]Patient was treated at multiple centres for her primary neoplasm.

^{||}Patients who presented during their SMN.

dysgenesis (45XO/46XY mosaic) received radioiodine for thyroid follicular cancer and developed osteosarcoma with a short latency of 0.2 years.

There were 2 other cases of solid SMNs in our cohort – osteosarcoma and atypical meningioma, occurring after Hodgkin's and Burkitt's lymphoma, respectively. Both lymphomas were treated with chemotherapy only.

Of the 12 patients who developed haematological SMNs (leukaemia and lymphoma), all but 2 had cytogenetic abnormalities (Table 3). Five of these cases (patients 3, 4, 8, 9 and 11) who were exposed to topoisomerase II inhibitor had involvement of 11q23, 11p15 or 21q22. Chromosome 7 deletion was noted in patient 14 but details of the chemotherapy received are not known to us. Patient 12 also displayed abnormal cytogenetics in her third malignancy of chronic myelomonocytic leukaemia (CMML) (not reflected in Table 3) involving 11q23 after receiving topoisomerase II inhibitors for her SMN.

Third Malignant Neoplasms

Following treatment for SMN, 2 patients developed a third malignancy. Patient 3 underwent treatment for secondary AML, including SCT which was complicated by chronic oral graft versus host disease, and developed squamous cell carcinoma (SCC) of the tongue 5.34 years after the SMN. He received standard treatment for the SCC. Patient 12 had CMML 1.28 years following diagnosis of secondary osteosarcoma and received metronomic therapy.

Outcome

Of all 15 patients with SMNs, 5 died of disease progression and 2 of treatment complications within 2 years of diagnosis of SMN/third malignancy. Patient 3 survived 6.16 years after AML (0.82 years after SCC) before succumbing to treatment complications of his third malignancy, while patient 12 survived 1.76 years following osteosarcoma (0.48 years after CMML) before succumbing to the disease. Of the 7 SMN survivors, 4 are alive with no evidence of disease while 3 have residual disease. Overall 5-year survival rate for SMNs was 41.0% (95% CI, 11.8% to 70.2%), significantly lower compared to 74% (95% CI, 71.1% to 76.9%) for primary malignancies ($P < 0.0005$) (Fig. 3).

Discussion

Several large scale cohort studies have provided vital information on epidemiology, risk factors and prognosis of patients with SMNs. The Nordic study (1943 to 2005) involving a population-based cohort of childhood cancer patients reported a 9% cumulative risk for SMNs at an attained age of 60,⁵ with leukaemia (26%), CNS

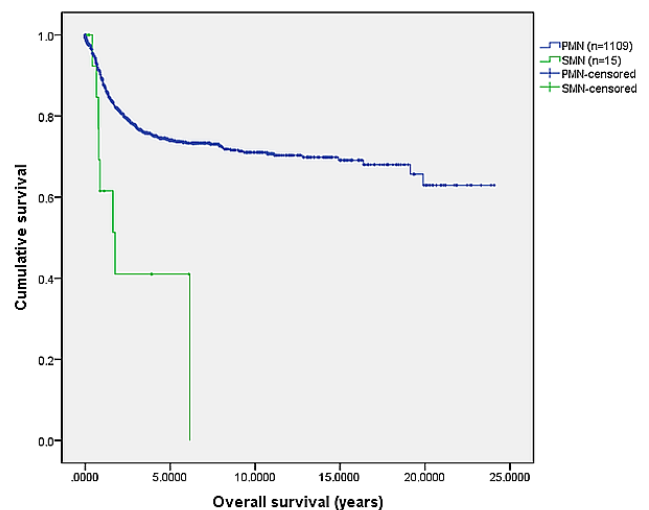


Fig. 3. Overall survival of patients with primary and secondary malignant neoplasms.

PMN: Primary malignant neoplasm, SMN: Secondary malignant neoplasm

neoplasm (23%), and lymphoma (13%) being the main primary malignancies. Similarly, the United States (US) Childhood Cancer Survivor Study (CCSS) (1970 to 1986) studied 5-year survivors of childhood cancer and reported a cumulative incidence of SMN of 3.2% at 20 years after diagnosis, with the main SMNs being breast cancer (22%), thyroid cancer (14%) and CNS tumours (11%).⁴ Beyond the West, a tertiary paediatric oncology centre in Hong Kong studied 1374 cases of childhood cancer treated from 1984 to 2009, with a 20-year cumulative incidence of 2.9%.¹⁴ The most common primary malignancies were leukaemia (44.6%), CNS (12.9%) and bone (8.2%) tumours. Of the 16 patients who developed SMNs, the most frequent SMNs were acute leukaemia/MDS ($n = 6$) and CNS tumour ($n = 4$).

The epidemiology of primary malignancies and SMNs in our centre-based cohort was found to be more similar to the Hong Kong study. The proportion of haematological SMN (leukaemias and lymphomas) in our cohort was 56.9%, comparable to Hong Kong (51%) and the US (54.5%), but substantially higher than the Nordic cohort (39.9%). The most common SMN in both our cohort and in Hong Kong was leukaemia, while solid tumours were predominant across the Nordic, US, British and Canadian cohorts.^{3-5,15} The pattern in SMN epidemiology is likely related to the epidemiology of primary malignancies and their respective treatments. In the Nordic and CCSS groups, more than a third (36% and 34%, respectively) of the primary malignancies were CNS tumours and lymphoma, where the mainstay of treatment is radiation-based. In contrast, haematological SMN is more related to exposure to specific chemotherapeutic agents for primary malignancies such as leukaemia and osteosarcoma

Table 3. Specific Chemotherapeutic Agents Received and Cytogenetic Profile of Patients with Secondary Acute Leukaemia or Lymphoma

No.	Primary Malignancy	Alkylating Agents		Platinum Compounds		Anthracyclines		Epipodophyllotoxins		SMN	Latency	Cytogenetics
		CPM (mg/m ²)	IFO (mg/m ²)	CDDP (mg/m ²)	DXR/DNR* (mg/m ²)	VP-16 (mg/m ²)	VM-26 (mg/m ²)					
1	ALL	8595.5	-	-	83.3	500	-	MPAL	3.0	MPAL	3.0	Complex karyotype [§]
2	ALL	1200	-	-	62.5	-	600	MPAL	12.7	MPAL	12.7	46,XX,t(2;14)(p11.2;q11.2)
3	ALL	1200	-	-	62.5	-	600	AML	12.8	AML	12.8	46,XY,t(8;21)(q22;q22)/46,XY
4	ALL	6000	-	-	353.3	-	-	AML	4.8	AML	4.8	46,XY,t(9;11)(p22;q23)/46,XY
5	ALL	-	-	-	-	-	-	NHL	1.8	NHL	1.8	46, XY
6†	Histiocytosis X	-	-	-	-	-	-	ALL	18.0	ALL	18.0	46-47,XX,der(7)t(7;12)(q32;q13), del(9)(p22)[12], ?inv(11)(q13q23), +14[6][cp15]/46,XX[5]
8	Osteosarcoma	-	-	480	450	-	-	MDS	1.9	MDS	1.9	46,XY,t(1;11)(q23;p15)
9	Osteosarcoma	-	36000	480	450	5000	-	AML	3.0	AML	3.0	46,XY,del(16)(p13.1),del(16)(q22), +(17)(q25), +(21)(q22)/46,XY
10	Osteosarcoma	-	55220	360	446.9	1500	-	AML	4.8	AML	4.8	47XX,+8,del(9)(q13q22)/48, idem, +del(9)/46XX
11	Osteosarcoma	-	44500	480	450	1500	-	AML	1.5	AML	1.5	46XX,t(9;11)(p22;q23)
13‡	ALL	-	-	-	-	-	-	AML	3.4	AML	3.4	46,XX
14‡	AML	-	-	-	-	-	-	ALL	1.9	ALL	1.9	46,XY,del(7)(q22q32)/46,XY

ALL: Acute lymphoblastic leukaemia; AML: Acute myeloid leukaemia; CDDP: Cisplatin; CPM: Cyclophosphamide; DNR: Daunorubicin; DXR: Doxorubicin; IFO: Ifosfamide; MDS: Myelodysplastic;

MPAL: Mixed phenotype acute leukaemia; NHL: Non-Hodgkin lymphoma; SMN: Second malignant neoplasm; VM-26: Teniposide; VP-16: Etoposide

*Daunorubicin converted into doxorubicin isotoxic dose using the formula: daunorubicin cumulative dose x 0.833 = doxorubicin isotoxic dose.

†Patient was treated at multiple centres for her primary neoplasm.

‡Patients who presented during their SMN.

§Significant abnormalities include del(5q), del(7q), del(9q), +(3q), +(8q) and +(17p).

and has a shorter latency than solid tumours. They may therefore represent a larger proportion of SMNs in studies with relatively short follow-up periods, such as in our study and Hong Kong.

The 20-year cumulative incidence of SMN was 5.3% in our cohort (January 1990 to April 2012), higher than that described in Western cohorts and in Hong Kong (2.9%) (May 1984 to June 2009). It is worth noting that with the exception of the population-based Nordic cohort, the other Western cohorts discussed above examined 5-year survivors. It has been observed that over 40% of SMNs occur within the first 5 years after diagnosis, and these were predominantly haematological SMNs.¹⁶ Studies that restricted participants to 5-year survivors may be underestimating the true risk of SMNs, especially secondary haematological malignancies with relatively short latency periods. Additionally, the Hong Kong study focused on patients who were treated 5 to 10 years earlier as compared to our cohort and were likely exposed to different types/intensities of treatments. Recent intensive therapeutic protocols may have improved cure rates of primary malignancies, increasing the incidence of SMNs as childhood cancer survivors live longer.

Most SMNs in our cohort occurred after ALL or osteosarcoma, with an increased risk associated with osteosarcoma. The 15-year cumulative risk of SMNs after ALL in our cohort is 4.4%, comparable to other studies describing overall risks from 3.3% at 15 years¹⁷ to 5.37% at 20 years¹⁸ and 5.2% at 25 years.⁴ In contrast, the 5-year cumulative incidence of SMN after osteosarcoma is 14.1%, substantially higher than a larger US centre that reported a 10-year cumulative incidence of 3.1%.¹⁹ The high incidence of SMN in our patients with osteosarcoma who were treated on a modified regimen derived from the same US centre, is of concern and warrants further study for risk factors that might be specific to our population.

Balanced chromosomal rearrangements are the hallmark of therapy-related leukaemia in patients treated with alkylating agents and topoisomerase II inhibitors. An analysis of the haematological SMNs in our cohort revealed cytogenetic features consistent with therapy-related malignancies. Topoisomerase II inhibitor use was a consistent feature and a likely major risk factor in our cohort. Since 2000, the epipodophyllotoxin teniposide has been removed from our treatment regimens for ALL. We have also revised our osteosarcoma protocols such that patients with metastatic osteosarcoma are no longer treated with additional ifosfamide and etoposide in view of recent data showing increased toxicities without improvement in outcomes.²⁰

Childhood cancer survivors continue to have increased overall mortality over the general population despite treatment.^{6,21-23} Not unexpectedly, we found that overall

survival of patients with SMNs was much poorer than in primary malignancies, with fewer than half surviving beyond 2 years. Our experience concurs with others that secondary AML carries poor prognosis and is often resistant to treatment, including SCT.¹⁰

This study is limited by several factors. The relatively short median follow-up of 3.49 years is just above the median latency for SMN development (3.41 years), hence SMNs that develop over time may be missed, underestimating the true risk of SMNs. Secondly, our data only captures patients from one centre and may not be representative of the overall population. Thirdly, the registry does not reflect other useful information such as treatment regimen, toxicities, complications and prevalence of hereditary cancer syndromes. Benign neoplasms may therefore be under-reported. Furthermore, the general weaknesses inherent to registry data research, including reporting delays, incomplete reporting and loss to follow-up, limits data accuracy. Nonetheless, reviewing clinical records for patients with SMNs ensured data accuracy in these patients. Future collaboration in a multicentre study may provide a larger study population.

Conclusion

This study demonstrated differences in the epidemiology of primary and SMNs, with haematological malignancies constituting the majority in our cohort as compared to solid tumours in the West. A significant risk of SMNs in patients with ALL and osteosarcoma was found, with SMN incidence in patients with osteosarcoma being particularly elevated compared to other centres. With topoisomerase II inhibitor use identified as a likely risk factor, modifications have already been made to our existing therapeutic protocols in osteosarcoma treatment. Other risk management strategies, including regular long-term surveillance, with early intervention for detected SMNs may serve to improve outcomes of patients at risk of SMN.

Acknowledgement

The authors would like to thank Miss Chua Hsin Chieh for her administrative support through the course of this research. They would also like to thank the team of doctors and nurses at the Khoo Teck Puat-National University Children's Medical Institute Paediatric Haematology-Oncology Unit for their dedication and care for patients with childhood cancer.

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