SHORT COMMUNICATION

Therapy Related AML/MDS Following Treatment for Childhood Cancer: Experience from a Tertiary Care Centre in North India

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Received: 29 March 2017 / Accepted: 15 June 2017 / Published online: 19 June 2017
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Abstract Therapy-related acute myeloid leukemia/myelodysplastic syndrome (t-AML/MDS) is a devastating late effect of cancer treatment. There is limited data on incidence of t-AML/MDS from India. We retrospectively studied pediatric t-AML/MDS at our institute between January 1996 and December 2015. Among 1285 children, 8 patients developed t-AML with a median age of 15.5 years. Overall incidence of t-AML/MDS was 0.62% [0.99% (4/402) in solid tumours and 0.45% (4/883) in leukemia/lymphoma, $P = 0.26$] with 6390 patient years of follow up. Primary malignancy included sarcoma [bone (2), soft tissue (2)], B-non-Hodgkin lymphoma (2) and acute lymphoblastic leukemia (2). The median cumulative equivalent doses of cyclophosphamide, doxorubicin and etoposide were 6.8, 270 and 2.5 gm/m² respectively. Two patients received radiotherapy [rhabdomyosarcoma (50 Gy), synovial sarcoma (45 Gy)]. The median latency period to develop t-AML/MDS was 24 months (range 16.5–62 months). Most common FAB morphology was M4/M5 (7/8) and cytogenetic abnormality was *MLL* rearrangement (4/8). Five patients opted for treatment, 4 achieved remission out of which 2 patients are alive and disease free. Short latency periods, absence of pre-leukemic phase and 11q23 translocations were characteristic

in the patients with t-AML/MDS. In view of poor outcome with conventional therapy, novel strategies and prevention need to be considered.

Keywords t-AML/MDS · Chemotherapy · Radiotherapy · Children · Malignancy

Abbreviations

t-AML/MDS	Therapy-related acute myeloid leukemia/myelodysplastic syndrome
FAB	French American British
NHL	Non-Hodgkin lymphoma
HL	Hodgkin lymphoma
ES	Ewing sarcoma
ALL	Acute lymphoblastic leukemia
BFM	Berlin–Frankfurt–Munster
LMB	Lymphomes malins B
SEER	Surveillance, epidemiology, and end results program

Introduction

Therapy-related acute myeloid leukemia/myelodysplastic syndrome (t-AML/MDS) is a well recognized, devastating complication of cancer treatment. Incidence of pediatric t-AML/MDS varies between 1 and 6% depends on the primary cancer and treatment exposure [1–3]. The outcome of these patients is often poor despite aggressive treatment. There is paucity of published data from India. Herein, we report the incidence, risk factors and outcome of eight patients who developed t-AML/MDS over a period of 18 years at our institute.

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Materials and Methods

This is a retrospective analysis of patients less than 18 years of age treated in the pediatric hematology-oncology unit of a tertiary care comprehensive cancer centre in North India. Medical records of patients who developed t-AML/MDS between January 1996 and December 2014, were identified from the hospital electronic database. Information pertaining to primary malignancy like age at diagnosis, gender, primary cancer, risk stratification/stage, treatment details including cumulative doses of alkylating agents, epipodophyllotoxins, anthracyclines, platinum compounds and radiotherapy were abstracted from the medical records. Follow-up data including date and status at last visit were also derived. Diagnosis of t-AML/MDS was confirmed by morphologic, cytochemical and immunophenotyping analysis of bone marrow aspirate and biopsy specimens. The French American British (FAB) cooperative group criteria were used to sub-classify the disease and cytogenetic and molecular studies were obtained. Treatment details, response and outcome of t-AML/MDS were also recorded.

Results

Amongst 1285 children treated during the study period, eight patients developed t-AML/MDS (6 males and 2 females). The incidence of t-AML/MDS was 0.62% [0.99% (4/402) for solid tumour and 0.45% (4/883) leukemia/lymphoma patients respectively, $P = 0.26$] with 6390 person-years of follow-up. The median follow-up of patients who were disease free at last contact was 52 months. The primary malignancy was sarcoma in 4 patients [one each had Ewing sarcoma (ES), osteosarcoma, rhabdomyosarcoma and synovial sarcoma] and hematolymphoid malignancy in 4 patients [two each had B-non-Hodgkin lymphoma (NHL) and acute lymphoblastic leukemia (ALL)]. Details regarding the primary cancer and therapeutic exposure as well as those pertaining to t-AML/MDS are summarized in Table 1. All the patients had received alkylating agents and/or anthracyclines while 5 were exposed to topoisomerase II inhibitors. The median cumulative doses of cyclophosphamide (equivalent), doxorubicin (equivalent) and etoposide were 6.8, 270 and 2.5 gm/m² respectively. Two patients received radiotherapy to the primary site. Presenting features of t-AML/MDS were persistent fever (6/8), gingival hyperplasia (5/8), bleeding (4/8), hepatomegaly and/or splenomegaly (3/8), leucocytosis >50,000/ μ l (5/8) and pre-leukemic phase (1/8). None of the patients had granulocytic sarcoma or central nervous system involvement. The dominant morphologic and cytogenetic features were FAB M4/M5 (4/8) and

presence of 11q23 translocation (4/8) respectively. The median age at presentation of t-AML/MDS was 15.5 years, with median latency period of 24 months. Five patients opted for treatment and 4 achieved morphological remission. Two patients died of infections and one from relapse 6 months after completion of treatment. The median survival was 5.5 months. Two patients are alive and disease free.

Discussion

In the present analysis, we report the incidence of t-AML/MDS to be 0.99 and 0.45% among pediatric patients with solid and hemato-lymphoid malignancy, respectively. This is data from a large comprehensive care cancer centre with a dedicated pediatric cancer unit that caters to patients from the Northern India. There is no published epidemiological data on the incidence of t-AML/MDS from India. Sandoval et al. [1], from St. Jude Children's Research Hospital reported an incidence of 1% (24/3696) in children treated over a 12 years period. Among 1201 patients with AML registered on protocol Children's Cancer Group 2891, 26 (2.2%) had t-AML/MDS [4]. Friedman et al. [5], have reported standardized incidence ratio of 6.0 for t-AML/MDS in 14,359 survivors of childhood cancer. Some of the variations in incidence are likely due to differences in follow up period and therapeutic exposure of the study population (Table 2).

The main agents implicated in the causation of t-AML/MDS include high cumulative doses of alkylating agents, topoisomerase II inhibitors and radiotherapy. Historically, the highest incidence of t-AML/MDS (4%) was noted in children treated for Hodgkin lymphoma (HL) [6]. We did not observe any case in our cohort of 167 Hodgkin lymphoma (HL) patients treated with doxorubicin, bleomycin, vinblastine and dacarbazine chemotherapy and involved field radiotherapy(selected subgroup) over 842 person-years of follow-up [7]. Recognition of various late effects in survivors of HL have led us and others to reduce the dose and field of radiotherapy as well as exposure to alkylating agents in contemporary protocols.

In our cohort of 463 ALL patients treated with the ALL-BFM 95 (Berlin–Frankfurt–Munster) protocol, the incidence of t-AML/MDS was 0.43%. This is similar to that reported by Möricke et al. [2, 8, 9] in their BFM 95 cooperative group trial (0.7%, 16/2169) as well as other studies across Europe and North America (2–3%).

The observation of t-AML/MDS among 2/146 (1.36%) patients with B-NHL treated on lymphomes malins B (LMB) 96 protocol was unenexpectedly more than in published literature. Bluhm et al. [10] reported 3 cases of

Table 1 Demographics, diagnosis, therapeutic exposures and outcome of primary cancer and t-AML/MDS

Patient no.	Age (years)/sex	Primary malignancy	Cyclo eq. dose (gm/m ²)	Etoposide (gm/m ²)	Doxo eq. dose (mg/m ²)	Latency (months)	FAB	Cytogenetics	Treatment	Survival (months)
1	11/M	Ewing sarcoma	28.3	4	375	21	M4	11q23	CT	20 ^a
2	13/M	Osteosarcoma	–	–	375	62	M2	Not done	No treatment	3
3	14/F	Rhabdomyosarcoma ^c	27.7	4	360	16	M5	11q23	CT+ autologous SCT	3.5 ^b
4	18/F	Synovial sarcoma ^d	13.17	1	300	50	M4	Complex	CT	9 ^e
5	4/M	Acute lymphoblastic leukemia	3	–	150	47	M2	Normal	CT+ allogenic SCT	35 ^e
6	13/M	Acute lymphoblastic leukemia	3	–	200	25	M2	Not done	No treatment	5
7	8/M	Non-Hodgkin lymphoma	6.8	2.5	240	23	M4	11q23	No treatment	6
8	17/M	Non-Hodgkin lymphoma	5.8	1.6	180	20	M4	11q23	CT	2 ^b

t-AML/MDS therapy-related acute myeloid leukemia/myelodysplastic syndrome, *No* number, *M* male, *F* female, *Doxo* doxorubicin, *Cyclo* cyclophosphamide, *Eq* equivalent, *FAB* French American British, *SCT* stem cell transplant

^a Death due to relapse, ^b toxic death, ^c radiotherapy exposure 50 Gy, ^d radiotherapy exposure 45 Gy, ^e alive and disease free

Table 2 Incidence of t-AML/MDS among survivors of childhood cancers: comparison with published literature

No.	Study	Authors	Treatment (year)	Total patients (n)	Follow up/total person (years)	Primary cancer	Latency (years) Median (range)	Patients with t-AML/MDS (n)	Cumulative incidence/SIR (95% CI)
1	CCSS	Friedman et al. [5]	1970–1986	14,359	30/325,119	ALL, AML, HL, NHL, astrocytoma, ES, OS, soft tissue sarcoma, NB, WT	7.4 (5–25)	21	NA/9.3 (6.1–14.3)
2	CCRG	Jenkinson et al. [19]	1926–1987	16,451	30/165,879	Leukemia, lymphoma, brain tumors, WT, OS, ES, RB, soft tissue tumors	6 (3–30)	17	NA/5.8 (3.6–8.6)
3	MDACC	Aguilera et al. [17]	1975–2007	2589	32/NA	HL, ALL, brain tumors, NHL, ES, NB, RMS	4.1 (1–9.9)	22	0.85%/NA
4	Multicentre	Schmiegelow et al. [18]	1980–2007	54,068	NA	ALL	2.7 (1.8–4.5)	255	0.47%/NA
5	CCSS	Bluhm et al. [10]	1970–1986	1082	27/NA	NHL	NA	3	NA/6.5 (1.3–18.9)
6	Present study		1996–2014	1285	NA/6390	ALL, NHL, OS, ES, soft tissue sarcoma	2 (1.3–5.1)	8	0.62%/NA

CCSS Childhood Cancer Survivor Study, CCRG (UK) Childhood Cancer Research Group (UK), MDACC MD Anderson Cancer Centre, ALL acute lymphoblastic leukemia, AML acute myeloid leukemia, NHL non-Hodgkin lymphoma, HL Hodgkin lymphoma, ES Ewing sarcoma, OS osteosarcoma, NB neuroblastoma, WT Wilms tumor, RB retinoblastoma, RMS rhabdomyosarcoma, SIR standardized incidence ratio, NA not available, *No* number, (*n*) total number, *CI* confidence interval

t-AML/MDS among 1082, 5-year survivors of NHL in the Childhood Cancer Survivor Study. Both our NHL patients received etoposide (cumulative doses, 1.6 and 2.5 g/m²) as part of LMB 96 group C therapy and their t-AML was characterised by presence of FAB M4/5 morphology and 11q23 translocation, known to be associated with its exposure. Various published data do indicate substantial risk of t-AML (>5%) for regimens that include higher cumulative doses of epipodophyllotoxins (9.2–19.0 g/m²) in a weekly or twice-weekly schedule [11, 12] and lower cumulative risks (<1.0%) with regimes without epipodophyllotoxins [8].

Children treated for solid tumors with epipodophyllotoxins (1.2–6 gm/m²) or anthracyclines (≥ 170 mg/m²) have been reported to have a sevenfold greater risk of t-AML/MDS [13]. Among patients with bone sarcoma we observed an incidence of 1.15% similar to that reported by others (2–6%) [3, 14]. The Childhood Cancer Survivor Study, observed significant correlation between high exposure to alkylating agents and occurrence of t-AML/MDS associated with deletion of chromosomes 5 or 7 among patients with ES [3]. While Pedersen-Bjergaard [15] reported that the risk of developing secondary leukemia increased 336-fold with etoposide doses above 2.0 g/m² compared to doses of 2.0 g/m² or less. We observed 11q23 translocation in both patients with sarcoma who received cumulative etoposide dose of 4 g/m². We did not study whether host pharmacogenetic factors may have played a role.

The survival was extremely poor as only 2 of the 8 patients survived after developing t-AML/MDS. Data from the surveillance, epidemiology, and end results program (SEER) registry as well as from other advanced centres report 5 years survival in the range of 20–40% [11, 16, 17]. The dismal outcome of t-AML/MDS emphasises the need for establishment of risk reduction strategies as well as novel treatments for this devastating condition. It is hoped that current efforts in precision medicine aimed at tumor and host related factors will alleviate the burden of cancer therapy and thereby reduce its incidence.

The main limitations of the present study are due to its retrospective nature, small size and short follow up. These may have led to under-estimation of actual incidence of t-AML.

Conclusions

We report the incidence of t-AML/MDS in a cohort of pediatric oncology patients from a single institution with 6390 person-years of follow-up. The incidence is similar to reports from other countries except for the unusual incidence among patients with NHL. Short latency, absence of

pre-leukemic phase, presence of 11q23 translocation and poor survival were characteristic of t-AML/MDS cases. It is hoped that the strategy of precision medicine in oncology would reduce the incidence of this devastating complication.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

Informed Consent Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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