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Original Article

Treatment Outcome for Therapy-related Myeloid Neoplasm in Children

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Abstract We report the clinical course and treatment outcome of 7 patients with therapy-related myeloid neoplasm in the past 32 years. The primary conditions included both solid tumours and leukaemia. The time interval between onset of primary disease and therapy-related neoplasm ranged from 1.2 years to 4.4 years. In contrary to the reported high treatment-related mortality and morbidity, with fludarabine-based salvage chemotherapy, stringent supportive care and early allogeneic stem cell transplantation as consolidative therapy, long term survival can be achieved in 5 out of 7 patients. Long-term follow-up is warranted for survivors with oncology patients who received chemotherapy.

Key words Myeloid Neoplasm; Therapy-related

Introduction

Therapy-related acute myeloid leukaemia (t-AML) / myelodysplastic syndrome (t-MDS) are now considered as a single disease entity, known as therapy-related myeloid neoplasm.[1] This disease entity has been reported to be associated with prior treatment with alkylating agents or epipodophyllotoxins with or without radiation for primary cancers.[2] The prognosis of therapy-related myeloid neoplasm remains grave. The 5-year overall survival is about 34% which is significantly lower than *de novo* acute myeloid leukaemia (AML) which is about 60%.[3] The chance of developing therapy-related myeloid neoplasm is dose related. With higher cumulative dose of alkylating agents in an Ewing Sarcoma study showed 16 fold increased risk of therapy-related myeloid neoplasm.[4,5] This is also one of the most frequent second malignant neoplasms in survivors of childhood cancers. For treatment in general, AML-type of salvage chemotherapy followed by allogeneic haematopoietic stem cell transplantation (HSCT) as post-remission consolidation therapy is usually recommended to achieve long term remission.[6]

In this report, we review our series of therapy-related myeloid neoplasm in terms of the clinical characteristics, treatment strategies and long-term outcome.

Method

A retrospective study of all therapy-related myeloid neoplasm cases over the past 32 years in a tertiary referral centre in Hong Kong was conducted.

The demographic data of primary diseases included the regimen and dosage of chemotherapy they had received, the dosage and site of radiotherapy (if received); the latency period between primary disease and onset of therapy-related myeloid neoplasm were reviewed.

For management of therapy-related myeloid neoplasm, the regimen and dosage of re-induction chemotherapy,

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transplant conditioning, transplant-related morbidity and the treatment outcome were analysed.

Results

Characteristics of Therapy-related Myeloid Neoplasm

From January 1985 to December 2017, a total of 212 new cases of AML and myelodysplastic syndrome (MDS) were diagnosed. Seven cases (3.3%) were identified to be therapy-related myeloid neoplasm. The primary diseases included 4 solid tumours (medulloblastoma, osteosarcoma, malignant peripheral nerve sheath tumour) and 3 haematological malignancies (2 acute lymphoblastic leukaemia, 1 non-Hodgkin lymphoma). The median age of diagnosis was 8.6 years old, ranged 5.5 to 16.7 years. The time interval between the onset of primary disease and diagnosis of therapy-related myeloid neoplasm ranged from 1.2 to 4.4 years with median of 3.2 years.

Cytogenetics study revealed monosomy 7 or deletion 7 in 4 cases, 11q23 translocation in one case and t(3;5) in another case.

Primary Treatment and Exposure History of Patients

Patient 1 was a 6.7-year-old boy with medulloblastoma. He received gross total tumour resection, craniospinal radiotherapy and systemic chemotherapy as curative therapy for primary disease. However, 4.4 years after the diagnosis, he suddenly developed pancytopenia and was diagnosed with therapy-related myeloid neoplasm. The neoplastic course was very refractory: he failed 2 courses of salvage chemotherapy and was eventually brought into remission by Gemtuzumab ozogamicin. He received unrelated cord blood transplant but unfortunately died of veno-occlusive disease of liver which was a treatment-related lethal complication.

Patient 2 was a 6.8-year-old boy with acute lymphoblastic leukaemia and was treated with systemic chemotherapy (CCLG 2008 Intermediate Risk Protocol). However, during his treatment period, he developed thrombocytopenia with re-appearance of blasts in the peripheral blood. He was diagnosed with therapy-related myeloid neoplasm at 1.8 years from initial diagnosis. He was treated with intensive chemotherapy and went into remission before unrelated cord blood transplantation. The disease was in control and now he is 4 years from transplantation.

Patient 3 was a 12-year-old girl with osteosarcoma. She received intensive chemotherapy (HKPHOSG Osteosarcoma Protocol) with limb-salvage surgery. The disease was under control but she developed pancytopenia 4.1 years from initial diagnosis. She was confirmed to have therapy-related myeloid neoplasm and the disease went into remission after salvage chemotherapy and she underwent unrelated stem cell transplantation. The disease has now been under remission for 10 years but she also suffered from serious chronic graft-versus-host disease (GVHD) of her lungs.

Patient 4 was another patient with acute lymphoblastic leukaemia patient. He was diagnosed when 13.2 years old. He was treated with systemic chemotherapy (CCCG 2015 Intermediate Risk Protocol) and the disease was in control. He developed pancytopenia during the treatment period and bone marrow study diagnosed secondary acute myeloid leukaemia 1.2 years from primary diagnosis. His disease was in remission again after salvage chemotherapy and he underwent human leukocyte antigen-matched sibling haematopoietic stem cell transplantation. The disease was in remission afterwards, but he developed relapse of therapy-related myeloid neoplasm at 1 year post-transplant. The disease was under control again with tapering off of immunosuppressive agents, donor-leukocyte infusion and commencement of venetoclax (BCL-2 inhibitor).

Patient 5 was a 2.4-year-old girl with malignant nerve sheath tumour of right thigh, she received systemic chemotherapy, curative surgery and local radiotherapy for control of her disease. Unfortunately, therapy-related myeloid neoplasm was diagnosed 2.2 years from diagnosis. She underwent unrelated cord blood transplantation and now has been disease free for 3 years.

Patient 6 was a 3.3-year-old patient with peripheral T-cell lymphoma who received systemic chemotherapy (IBFM 2002 High Risk Protocol) and the disease was under control. However, therapy-related myeloid neoplasm was diagnosed 2 years from initial diagnosis and she underwent unrelated cord blood transplantation. This year is her tenth year of disease-free survival.

Patient 7 was a 4.3-year-old patient with stage IV neuroblastoma who received systemic chemotherapy (Modified N7 Neuroblastoma Protocol), surgery, radiotherapy to abdomen (primary site), MIBG (12 mCi / kg) therapy with megadose chemotherapy and stem cell rescue. However, the disease relapsed after he had received these curative therapies. Moreover, he also developed this secondary event at 3.9 years from diagnosis. In view of the very poor pre-morbid condition and because the prognosis was extremely grave. He received palliative care and eventually died of this secondary fatal event.

The details of the treatment histories of these patients are summarised in Tables 1 and 2.

Discussion

Therapy-related myeloid neoplasm is one of the common second malignancies after treatment for primary cancers.[7,8] In our previous study of all patients who had received anti-cancer treatment, the cumulative incidence of second cancer is 2.9% at 20 years, and therapy-related myeloid neoplasm was the commonest type of second malignancy.[8] All our patients received alkylating agents and epipodophyllotoxins during the treatment for the primary cancers. Two patients had also received radiotherapy for local control of solid tumours. The interval between primary cancers to onset of therapy-related myeloid neoplasm was 1.2-4.4 years, thus long term follow-up of cancer survivors is necessary to detect such late complications. Therapy-related myeloid neoplasm has poorer prognosis when compared with *de novo* AML/MDS when treated with chemotherapy only. Imamura et al who recently reported the outcome of 43 paediatric patients with therapy-related acute lymphoblastic leukaemia and therapy-related myeloid neoplasm demonstrated that allogeneic HSCT was associated with superior 5-year overall survival [78.8% (with HSCT) vs 12.1% (without HSCT)], $p<0.001$].[9] In our review, we also observe that the majority of patients who could achieve remission or had stable disease and underwent allogeneic HSCT in a timely manner, could achieve long term remission. Early HSCT will decrease the exposure of prolonged intensive chemotherapy before transplant and may reduce the transplant-related toxicity. We adopt early HSCT approach with unrelated cord blood transplant and utilise double unit cord blood if single unit cord blood has suboptimal cell dose. Patients can undergo HSCT at 2.5 to 3 months from diagnosis of therapy-related myeloid neoplasm.

However, special attention needs to be made on these patients, as they were previously treated with intensive chemotherapy, we need to be cautious about treatment related toxicity of salvage chemotherapy and conditioning

Table 1 Baseline demographics and primary disease treatment data

Patients	Primary Diagnosis	Exposure to Alkylating Agents (Cumulative Dose)	Exposure to Anti-tumour Antibiotics (Cumulative Dose)	Exposure to Topoisomerase Inhibitors (Cumulative Dose)	Exposure to Radiation (Site / Dose)	Age at Diagnosis of Therapy-related Neoplasm (Years)	Time from Primary Diagnosis (Years)
1	Medulloblastoma	Lomustine (600 mg/m^2) Cisplatin (600 mg/m^2)	–	–	Craniospinal (55.8 Gy)	11.1	4.4
2	Acute Lymphoblastic Leukaemia	Cyclophosphamide (4 grams/m^2)	Adriamycin (250 mg/m^2)	–	–	8.6	1.8
3	Osteosarcoma	Ifosfamide (37.5 grams/m^2)	Adriamycin (420 mg/m^2)	Etoposide (1500 mg/m^2)	–	16.7	4.1
4	Acute Lymphoblastic Leukaemia	Cyclophosphamide (4 grams/m^2)	Adriamycin (250 mg/m^2)	–	–	14.4	1.2
5	Malignant Peripheral Nerve Sheath Tumour	Ifosfamide (54 grams/m^2)	Adriamycin (375 mg/m^2)	–	Right thigh (55.8 Gy)	5.6	3.2
6	Peripheral T-cell Lymphoma (NHL)	Ifosfamide (4 grams/m^2) Cyclophosphamide (4.5 grams/m^2)	Adriamycin (390 mg/m^2)	Etoposide (500 mg/m^2)	–	5.5	2.2
7	Stage IV Neuroblastoma	Cyclophosphamide (420 mg/kg), Cisplatin (400 mg/m^2)	Adriamycin (225 mg/m^2)	Etoposide (1200 mg/m^2)	Abdomen (21 Gy)	8.2	3.9

NHL=Non-hodgkin Lymphoma

Table 2 Treatment data and outcome

Patient	Cytogenetics	Chemotherapy	Disease Status Pre-transplant	Time Interval from Diagnosis to Transplant	Treatment	Conditioning	Treatment-related Complications	Outcome
1	45XY, t(3;3) (q21,126.3), -7	Failed 2 courses of AML96, then given Mylotarg for 2 doses	In remission	3.5 months	Unrelated Double unit Cord blood transplant	Fludarabine (150 mg/m^2) / Melphalan (140 mg/m^2) / ATG	Liver VOD	Died at 2 months post-HSCT due to VOD of liver
2	t(9;11) (p22,q23)	NOPHO-AML (2 inductions and 1 consolidtion)	In remission	3.8 months	Unrelated Double unit Cord blood transplant	Cyclophosphamide (120 mg/kg) / Busulfan / Melphalan (140 mg/m^2) / ATG	AGVHD II (skin, gut) / Skin CGVHD	Cytogenetic remission and CR at 4 years post-HSCT Lansky Score: 80
3	46 XX, del(7)(q31)	FLAG for 1 course (Fludarabine, Cytarabine), complicated with severe neuropathies, required ICU care and mechanical ventilation	In remission	3.2 months	Unrelated PBSC transplant	Cyclophosphamide (120 mg/kg) / Busulfan / Melphalan (140 mg/m^2) / ATG	AGVHD III (gut) / Severe Lung CGVHD	Cytogenetic remission and CR at 10 years post-HSCT Karnofsky Score: 30
4	79XXYY, del (4,7,9,16)	FLAG for 2 courses (Fludarabine, Cytarabine)	In remission	2.9 months	HLA-identical sibling transplant	Cyclophosphamide (120 mg/kg) Busulfan / Melphalan (140 mg/m^2)	AGVHD II (skin, gut)	Cytogenetic remission and now post-transplant 1 year with relapse, salvage with tapering immunosuppressive agents, donor leukocyte infusion and venetoclax (BCL-2 inhibitor), now in remission again
5	46XX, t(3;5) (q25;q34)[14]/ 46, idemi(17) (q10)[6]	No chemotherapy	Refractory anaemia with excess blast (19%)	2.5 months	Unrelated Double unit Cord blood transplant	Cyclophosphamide (120 mg/kg) / Busulfan / Melphalan (140 mg/m^2) / ATG	AGVHD Grade II (gut)	Cytogenetic remission and CR at 3 years post-transplant Lansky Score: 80
6	46XX, del (7)(q22)	Cytarabine (80 mg/m^2 for 5 days), 6-mercaptopurine (70 mg/m^2 for 5 days), in every 21 days for total 2 courses	Refractory cytopenia with unilineage dysplasia	2.6 months	Unrelated Double unit Cord blood transplant	Cyclophosphamide (120 mg/kg) / Busulfan (16 mg/kg) / Melphalan (140 mg/m^2) / ATG	AGVHD Grade II/ Limited skin CGVHD	Cytogenetic remission and CR at 10 years post-transplant Lansky Score: 100
7	NA	6-mercaptopurine/ methotrexate	Palliative therapy	–	–	–	–	Died of active disease

AML=acute myeloid leukaemia; ATG=antithymocyte globulin; VOD=veno-occlusive disease of liver; AGVHD=acute graft-versus-host disease; HSCT=haematopoietic stem cell transplantation; CGVHD=chronic graft-versus-host disease; CR=complete remission; HLA=human leukocyte antigen; PBSC=peripheral blood stem cell; FLAG=fludarabine cytarabine; ICU=intensive care unit; NA=not available

regimen. Gassas et al reported that fludarabine cytarabine with or without idarubicin was the most common salvage protocol, and it achieved complete morphological remission in 28 out of 36 patients before HSCT. However, the post-transplant treatment-related mortality was about 60%. Transplant-related mortality was the leading cause.[10,11] In our series, with the policy of stringent infection control practice and close monitoring of organ dysfunction with timely intervention with defibrotide for early veno-occlusive disease of liver (VOD), only one patient (Patient 1) died at early post-transplant period because of this complication. Craniospinal irradiation and Gemtuzumab ozogamicin before transplant are risk factors for VOD. However, the major complication in our series was GVHD. Sixty-six percent had grade II-III acute GVHD and 3 out of 5 (60%) patients who survived had chronic skin or lung GVHD. Two patients had only limited chronic GVHD and there was no significant impact on patients' daily function. However, patient 3 suffered from very serious chronic lung GVHD which significantly affected her daily function.

Karyotype is an independent prognostic parameter in therapy-related myeloid neoplasm. When compared with *de novo* AML, 26.9% of therapy-related myeloid neoplasm vs 11.3% of *de novo* AML patients expressed complex aberrant karyotypes. For 11q23, 12.9% of therapy-related myeloid neoplasm vs 3.7% of *de novo* AML patients demonstrated this cytogenetic abnormality.[12] In our series, one third expressed monosomy 7 and one case showed complex aberrant karyotype. One had monosomy 7 and two had deletion 7 abnormalities, one patient had 11q23 abnormality while another one with complex karyotyping abnormalities. These adverse karyotypes were proven to be independently related to overall survival (p=0.001). Within patients with therapy-related myeloid neoplasm, there were significant correlations with overall survival.[12]

Conclusion

Although therapy-related myeloid neoplasm is uncommon, it can happen in long-term survivors of childhood cancers, long-term follow up of cancer survivors is therefore warranted. With fludarabine-based salvage chemotherapy, stringent supportive care and early allogeneic stem cell transplantation as consolidative therapy, long term survival can be achieved in a high proportion of patients.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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