ACUTE MYELOID LEUKAEMIA WITH DOWN SYNDROME: A CASE SERIES ON THE USE OF VINCRISTINE

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Abstract

Myeloid Leukemia with Down Syndrome (ML-DS) is a unique entity of AML with superior treatment response and overall survival compared to children with AML. Despite all of it, ML-DS survival rates for children in low- and middle-income countries (LMICs) remain poor. We described three ML-DS cases, which were treated with vincristine, cytarabine and daunorubicin plus triple intrathecal drugs. All of our three patients successfully finished the treatment, with two patients were still complete remission until now, and one died two days after finishing the chemotherapy. ML-DS is treatable in our limited-resources setting in Manado, Indonesia.

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Abbreviations

AML	Acute Myeloid Leukemia
ML-DS	Myeloid Leukemia with Down Syndrome
LMICs	Low- and middle-income countries
DS	Down Syndrome
AMKL	Acute Megakaryoblastic Leukemia
ALL	Acute Lymphoblastic Leukemia
Ara-C	Cytarabine
HD-araC	High Dose Cytarabine
OS	Overall Survival
EFS	Event-Free Survival
ANC	Absolute Neutrophil Count

ABSTRACT

Myeloid Leukemia with Down Syndrome (ML-DS) is a unique entity of AML with superior treatment response and overall survival compared to children with AML. Despite all of it, ML-DS survival rates for children in low- and middle-income countries (LMICs) remain poor. We described three ML-DS cases, which were treated with vincristine, cytarabine and daunorubicin plus triple intrathecal drugs. All of our three patients successfully finished the treatment, with two patients were still complete remission until now, and one died two days after finishing the chemotherapy. ML-DS is treatable in our limited-resources setting in Manado, Indonesia.

MAIN BODY OF TEXT

INTRODUCTION

Children with Down Syndrome (DS) have a 10- to 20- fold increased risk of developing acute leukemia. The relative risk of developing acute megakaryoblastic leukemia (AMKL) is estimated to be 500 times higher in children with DS than in those without DS.[1] The natural history of leukemia in children with DS suggests that trisomy 21 directly contributes to the malignant transformation of hematopoietic cells, and somatic mutations of the GATA1 gene have been detected in nearly all ML-DS cases. Other types of acute leukemia occurs in children with DS, do not have GATA1 mutation and concers either ALL or AML. Only ML-DS is highly suspectible to chemotherapy[2,3].

In Asia, the overall survival for ML-DS in Japan is approximately 80%.[4] Retrospective review from 19 patients with ML-DS in Hong Kong, showed a favorable 5-years event-free and overall survival of 89.5% and 89.5%, respectively.[5] The survival rates for children in low- and middle-income countries (LMICs) remain poor[6], but there was no report so far regarding the AML-DS survival rate in LMICs country in Asia.

Here we reported three cases of ML-DS in limited resources pediatric oncology center in Manado, Indonesia with an innovative combination of vincristine, daunorubicin, and cytarabine.

2. CASE DESCRIPTION

Case 1: ARA is a 1 year 5 months old girl, admitted to the hospital looking pale and with fever. Physical findings were that of anemia and hepatosplenomegaly. Blood counts showed hemoglobin of 4.4 g/dL, leucocytes of 51,840/mm^3, and platelets of 5,000/mm^3. The peripheral blood smear showed domination of lymphoblast cell (71%), the lymphocyte size was big, without any granule, and no Auer rods appearance, with impression of Acute Lymphoblastic Leukemia (ALL) and the bone marrow aspiration showed a 26% blast with morphology of ALL. The immunophenotyping was positive for the myeloid lineage. DNA analysis for GATA-1 mutation is not available due to laboratory issue. She was treated using ML-DS protocol, consisting of triple intrathecal (methotrexate, dexamethasone, and ara-C) on day 1, vincristine (1.5 mg/m^2 i.v, max 2 mg) on day 1 and day 8, daunorubicin (50 mg/m^2/day i.v) on day 8, and cytarabine (100 mg/m^2/dose i.v pushed twice a day) on day (see figure 1) 8 to 12. The course was given twice, with an interval of 3 to 4 weeks (Figure 1). Upon diagnosis the blood count profile was hemoglobin 13.3 g/dL, leucocytes of

10.730/mm^3, and platelets 241.000/mm^3. The leucocytes levels on day 8th of treatment was 4.407/mm^3. She experienced febrile neutropenia once and delayed in chemotherapy schedule. Till date, she is surviving for 46 months.

Case 2: MBC is a 1 year 9 months old girl, admitted to the hospital looking pale and with fever. Physical findings were that of anemia, pansystolic murmur, and hepatosplenomegaly. Blood counts showed hemoglobin of 2.8 g/dL, leucocytes of 4,500/mm^3 and platelets of 10,000/mm^3. Echocardiography showed an atrial septal defect. The initial blood smear shown an relative lymphocytosis. On bone marrow aspiration showed 75.5% myeloblast with morphology of AML-M2. The immunophenotyping was positive for the myeloid lineage of the blasts. DNA analysis was positive for GATA-1. She was treated using the same protocol, initial laboratory before the start of chemotherapy was hemoglobin 7.6 g/dl, leucocyte 7.471 /mm3, platelets 10.000 /mm3. On day 8th of chemotherapy, the leucocyte level was 2.399 /mm^3. Along the course of treatment, the patient experienced one episode of severe febrile neutropenia, and several times of severe thrombocytopenia. However, the patient died because of uncontrolled bleeding two days after the completion of therapy.

Case 3: AKY is a 2 years and 2 months old boy, admitted to hospital with fever. The physical finding was that of hepatosplenomegaly. Blood counts showed hemoglobin of 11.9 g/dL, leucocytes of 8,640/mm^{3,} and platelets of 2,000/mm^3. The peripheral blood smear shown a 33% myeloblasts without maturation, with morphology of AML-M5a, and the bone marrow aspiration shown 76% of myeloblasts with characteristics of AML-M5b. The immunophenotyping was positive for myeloid lineage. Cytogenetics showed Trisomy 21. The DNA analysis for GATA-1 mutation was positive. He was treated using the same AML-DS Protocol. Upon admission the hemoglobin was 8.8 g/dl, leucocyte 88.800 /mm3, platelets of 13.000 /mm3, on day 8 blood counts profile was Hb 11.1 g/dl, leucocyte 83.000 /ul, platelets of 20.000/ul. The patient experienced febrile neutropenia twice, severe thrombocytopenia once, and malaria infection. Until now, he is surviving for 30 months.

Along the course of treatment, all of the patients receive a supportive transfusion of packed-red cells and thrombocyte. Bacterial and fungal infection prophylaxis was given with amoxicillin-clavulanic acid and ketoconazole. The total cumulative doses for cytarabine is 2000 mg/m^2, daunorubicin is 40 mg/m^2 and vincristine is 6 mg/m^2.

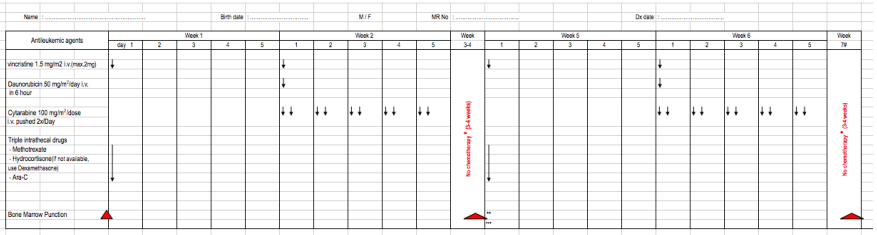

Figure 1. Myeloid Leukemia Protocol

3. DISCUSSION

We present three cases of ML-DS, of whom two are in continuous complete remission until now, and one died on the last day of the chemotherapy treatment. We used a two-cycle protocol using systemic vincristine, daunorubicin, and cytarabine (ara-C) plus triple intratechal chemotherapy.

Vincristine has been a standard of chemotherapy regimens for many childhood cancers but was rarely used especially in patient with AML and ML-DS.[8] A study in Japan showed vincristine was toxic to the terminal divisions and self-renewal of the AML blast progenitor within in-vitro setting. The results showed vincristine can inhibit the growth of blast progenitors in dose- and time-dependent manners. In the repeated exposure, only vincristine in high-dose shown a reduction of clonogenic cells. Suggesting if vincristine combined with other drugs, the success of treatment can be achieved easily.[9]

Recent in-vitro study for drug resistance profile shown the ML-DS cells were significantly more sensitive to cytarabine, anthracyclines, etoposide, and vincristine. This study suggested the benefit of vincristine in ML-DS, as this drug had the highest toxicity to the ML-DS blast cells.[10] Our patients who were treated using vincristine, cytarabine and daunorubicin showed an improvement in blood counts profile after the first cycle of chemotherapy, suggesting the efficacy of these drugs combinations. Vincristine was also well tolerated by children with DS variant of leukemia.[11,12]

Al Ahmari et al.[13] used vincristine for their ML-DS patients, comparing between a very low-dose, long-term ara-C regimen, and standard High-dose ara-C (HD-ara-C) regimens from contemporary protocols. The low dose regimen consisted of ara-C 10 mg/m^2 twice-a-day subcutaneous injection for 7 days, with vincristine 1 mg/m^2 and retinylpalmitate 25,000 units/m^2/day. This regimen was repeated every 2 weeks for 2 years, with 5-years EFS between low-and high-dose regimens not being different at all (67 and 75%, respectively) and neither was the OS (77 and 80%, respectively).

Chidren's Oncology Group AAML0431 trial for AML-DS patients was focusing on curative chemotherapy dose intensity while minimizing treatment-related toxicity with ara-C and daunorubicin. The treatment protocol consists of 4 induction cycles and 2 intensification therapy cycle, with HD-ara-C was used in the second induction and 25% dose reduction in daunorubicin. For 204 patients, 5-year EFS was 89.9% and overall survival was 93%. Prolonged ANC recovery, severe febrile neutropenia and severe sterile-site bacterial infection were common.[14]

The ML-DS 2006 trial focused on therapy reduction intensity using a lower cumulative dose of chemotherapy. This trial applied intrathecal CNS prophylaxis without any maintenance therapy and still showed a satisfying result. The total cumulative dose of cytarabine was 27,400 mg/m2 instead of 29,400 mg/m^2 used in AML-BFM 98 trial, meanwhile etoposide was 450 mg/m^2 rather than 950 mg/m^2. The results of this trial showed a 5-year overall survival rate (OS) of 89%, EFS of 87%, and cumulative incidence of relapse/nonresponse of 6% $\pm$ 3%; similar to the historical control arm (AML-BFM 98) which consist of longer duration and a higher dose of therapy.[15] We use an even lower cytarabine with total cumulative dosage 2,000 mg/m^2, and also omitting maintenance therapy, but with vincristine added to cytarabine and daunorubicin. Where we have a good result as well, but in only two patients.

Another study from Brazil, as one of LMICs, reported ML-DS patients (age $<$ 19 years old) had a survival rate of 62.5%. The patients received two induction cycles chemotherapy of daunorubicin, cytarabine and etoposide followed by low-dose cytarabine for 21 days.[6] We used an innovative regimen with regular dose of vincristine, ara-C and daunorubicin for a shorter duration with a good result, although the patient number is small.

In conclusion, ML-DS is curable in LMICs with limited resources pediatric oncology setting like Indonesia. Further study of more patients is needed to evaluate the effectiveness of our protocol.

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The authors stated that there is no conflict of interest in this study, which might be perceived as posing a conflict or bias.

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