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ORIGINAL ARTICLE

Long-term outcome for Down syndrome patients with hematopoietic disorders

Meng-Ju Li [a], Ni-Chung Lee [b,c], Yung-Li Yang [b,d], Hsiu-Ju Yen [e], Hsiu-Hao Chang [b], Yin-Hsiu Chien [b,c], Meng-Yao Lu [b], Shiann-Tarng Jou [b], Kai-Hsin Lin [b], Wuh-Liang Hwu [b,c], Dong-Tsamn Lin [b,*]

[a] *Department of Pediatrics, National Taiwan University Hospital Hsin-Chu Branch, Hsinchu, Taiwan*
[b] *Department of Pediatrics, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan*
[c] *Department of Medical Genetics, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan*
[d] *Department of Laboratory Medicine, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan*
[e] *Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan*

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Background/purpose: Although Down syndrome (DS) patients have a higher risk of developing transient myeloproliferative disorder (TMD) and acute leukemia, very little data is available on long-term outcome in Taiwanese patients. The current study was designed to determine the clinical characteristics and treatment outcome of DS patients with TMD or acute leukemia (AL).

Methods: In 25 consecutive DS patients with TMD or AL enrolled from 1990 to 2012, clinical manifestations and treatment protocols were investigated and *GATA1* (GATA binding protein 1) mutations were identified. Among 16 DS-acute myeloid leukemia (DS-AML) patients, clinical outcomes were compared between survivors and nonsurvivors.

Results: Most of our DS patients had TMD (32%), acute megakaryoblastic leukemia (24%), or acute erythromegakaryoblastic leukemia (16%). The median follow-up time was 22.5 months (1–230 months). The age was younger and the hemoglobin (Hb) level and platelet count were higher in TMD patients than in leukemia patients. Among DS-AML patients, the Hb level was higher in survivors than nonsurvivors (8.8 $\pm$ 2.7 g/dL vs. 5.8 $\pm$ 2.4 g/dL; $p = 0.044$) and the age was older in relapsed patients than in nonrelapsed patients (43.8 $\pm$ 18 months old vs. 21.6 $\pm$ 8.6 months old; $p = 0.025$). The 3-year overall survival (OS) rate was 44%, higher in patients receiving appropriate chemotherapy than in those receiving inadequate treatment

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* Corresponding author. Department of Pediatrics, National Taiwan University Hospital and College of Medicine, National Taiwan University, Number 7, Chung-Shan South Road, Taipei, 100, Taiwan.
E-mail address: dtlin@ntu.edu.tw (D.-T. Lin).

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(63.6% vs. 0%, $p = 0.001$), and higher in those diagnosed with TMD or AL after 2008 than before 2008 (33.3% vs. 75%; $p = 0.119$).
Conclusion: Outcome in DS-AML patients is optimal if appropriate treatment is provided. With modification of the treatment strategy in 2008, OS increased in Taiwan.

Introduction

Trisomy 21 [Down syndrome (DS); MIM #190685; a common chromosome aneuploidy] is associated with an increased risk of early-onset hematopoietic disorders.[1] Around 10% of newborns with DS develop transient myeloproliferative disorder (TMD).[2] DS children have a 50-fold increased incidence of acute leukemia during the first 5 years of life.[3,4] The acute leukemias in approximately 60% of affected DS children are myeloid, with at least 50% of these being acute megakaryoblastic leukemia (AMKL).[5] Mutations in exon 2 of the *GATA1* (GATA binding protein 1) gene, resulting in a premature stop codon within the N-terminal activation domain (i.e., GATA1s, a truncated form of GATA1) have been detected in almost all TMD and DS AMKL cases.[6–9] Both GATA1s and GATA1 have similar DNA binding abilities and interact with partner proteins, such as ''Friend of GATA1'' (FOG1).[10] Expression of this mutated form potentially contributes to the uncontrolled proliferation of poorly differentiated megakaryocytic precursors.[11]

Acute myeloid leukemia (AML) in patients with DS is referred to as myeloid leukemia associated with DS (DS-AML) in the 4th edition of the World Health Organization classification.[4] The overall survival (OS) of DS-AML patients is approximately 80%.[12–19] However, more accurate prenatal screening in Taiwan in recent years has led to fewer DS births, and fewer DS-TMD or DS-acute leukemia (DS-AL) cases are available for study. In general, the treatment protocols for DS-AL patients are based on the recommendations of the Taiwan Pediatric Oncology Group (TPOG). Because reports of clinical presentations or long-term outcome in the early period are sporadic and few in number,[20–23] the present study aimed to investigate the long-term outcome in Taiwanese patients with DS-TMD or DS-AL and to determine the risk factors for DS-TMD or DS-AL.

Methods

Patients and sample collection

We retrospectively reviewed the medical records of 25 consecutive DS patients with hematopoietic disorders diagnosed in our hospital (or whose samples were sent to our hospital for *GATA1* mutation analysis) from 1990 to 2012. DS was diagnosed shortly after birth using karyotype analysis and clinical manifestations. TMD was diagnosed before the age of 3 months by the presence of peripheral blood nonerythroid blasts and by reduction in the peripheral blood blast cell percentage occurring in response to cytoreductive therapy or spontaneously.[24] Acute leukemia was diagnosed by morphologic, biochemical, immunophenotypic, and cytogenetic analysis of bone marrow or peripheral blood and classified according to French–American–British (FAB) criteria.[25] Age at onset, sex, initial white blood cell count, blast percentage, hemoglobin (Hb) level, platelet count, levels of alanine transaminase, aspartate transaminase, lactate dehydrogenase, and uric acid, karyotype results, immunophenotyping results, treatment regimens, and outcomes were all retrospectively obtained from the charts. Study protocol approval was obtained from our institutional ethics committee (No. 201312034RINC).

Chemotherapy

The treatment protocols for DS with AL are based on the recommendations of the TPOG and include the standard protocol for acute lymphoblastic leukemia,[26] and several modifications of the standard protocol for *de novo* AML (i.e., the TPOG AML 901 protocol, AML 97A protocol, and AML 97B protocol before and during 2008 and the TPOG AML-DS 2008 protocol after 2008).[27] The protocol-specified treatment periods were approximately 1 year.

The TPOG AML 901 protocol used since 1990 consisted of three steps: induction [i.e., treatment with epirubicin, cytosine arabinoside (Ara-C), and 6-thioguanine (6-TG)]; consolidation (i.e., treatment with etoposide and cyclophosphamide), and maintenance [i.e., treatment with epirubicin, Ara-C, 6-TG, etoposide, cyclophosphamide, mercaptopurine, and methotrexate (MTX)]. The AML 901 protocol was revised in 1997 and the resulting AML 97A and AML 97B protocols differed from their predecessor as follows. The AML 97B protocol consisted of the same three steps but used idarubicin instead of epirubicin and added mitoxantrone. The AML 97A protocol consisted of only two steps: induction with Ara-C and idarubicin, and post-remission with high-dose Ara-C (1 g/m^2), etoposide, mitoxantrone, and idarubicin. The DS 2008 protocol used the half dose regimen of the AML 97A protocol but reduced the Ara-C dose by 25%, added intrathecal MTX to the induction regimen, and used L-asparaginase instead of mitoxantrone in the AML 97A consolidation regimen. In our study, use of either the full- or half-dose AML 901, AML 97A, or AML 97B protocols and the AML DS 2008 protocol in DS-AML patients was regarded as *standard treatment*. The use of palliative or partial treatment was regarded as *incomplete treatment*. Our patients were followed up from January 1990 to June 2014 inclusively. The duration of OS was measured from the time of diagnosis to the date of death or last follow up.