Natural history of transient myeloproliferative disorder clinically diagnosed in Down syndrome neonates: a report from the Children’s Oncology Group Study A2971

Alan S Gamis¹, Todd A Alonzo², Robert B Gerbing ³, Joanne M Hilden⁴, April D Sorrell⁵, Mukta Sharma¹, Thomas W Loew⁶, Robert J Arceci⁷, Dorothy Barnard⁸, John Doyle⁹, Gita Massey¹⁰, John Perentesis¹¹, Yaddanapudi Ravindranath¹², Jeffrey Taub¹², Franklin O Smith¹¹.

¹ Children's Mercy Hospital & Clinics, Kansas City, MO; ²Univ of Southern California, Los Angeles, CA; ³Childrens Oncology Group, Arcadia, CA; ⁴Children’s Hospital Colorado, Denver, CO; ⁵City of Hope, Duarte CA; ⁶University of Missouri, Columbia, MO; ⁷Johns Hopkins University, Baltimore, MD; ⁸IWK Health Center, Halifax, Nova Scotia; ⁹Hospital for Sick Children, Toronto, Ontario, Ca; ¹⁰Virginia Commonwealth University, Richmond, VA; ¹¹Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; ¹²Children's Hospital of Michigan, Detroit, MI

Corresponding Author: Alan S Gamis, MD, MPH
Children’s Mercy Hospitals & Clinics
2401 Gillham Rd
Kansas City, MO 64108
Telephone: 816-234-3265
Fax: 816-855-1700
Email: agamis@cmh.edu

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Abstract

Transient Myeloproliferative Disorder (TMD), restricted to newborns with trisomy 21, is a megakaryocytic leukemia that while lethal in some is distinguished by its spontaneous resolution. Later development of acute myeloid leukemia (AML) occurs in some. Prospective enrollment (n=135) elucidated the natural history in DS patients diagnosed with TMD using uniform monitoring and intervention guidelines. Prevalent at diagnosis were leukocytosis, peripheral blast exceeding marrow blast percentage, and hepatomegaly. Among those with life-threatening symptoms (LTS), most (n=29/38 (76%)) received intervention therapy until symptoms abated and then monitored similarly. Organomegaly with cardiopulmonary compromise most frequently led to intervention (43%). Death occurred in 21% but only 10% were due to TMD (intervention vs. observation patients: 13/14 vs. 1/15 due to TMD). Among those solely observed, peripheral blasts and all other TMD symptoms cleared at a median of 36 and 49 days from diagnosis, respectively. Based upon the diagnostic clinical findings of hepatomegaly with or without LTS, 3 groups were identified with differing survival: low risk with neither finding (38%), intermediate risk with hepatomegaly alone (40%), and high risk with both (21%) (OS - 92±8%, 77±12% and 51±19% respectively (p≤0.001). Among all, AML subsequently occurred in 16% at a median of 441 days (118-1085 days). The trial is registered at www.clinicaltrials.gov as NCT00003593.

Introduction

Neonates with Down syndrome (DS) have a unique predilection to develop Transient Myeloproliferative Disorder (TMD), a rare clonal myeloproliferation characterized by peripheral leukocytosis indistinguishable at presentation from acute megakaryocytic leukemia (AMKL), FAB M7, or AML with minimal differentiation, FAB M0. Its predilection for DS neonates coupled with its unique characteristics of a relative paucity of leukemic blasts within the marrow, variable pancytopenia, a propensity for mild to life-threatening hepatic infiltration, and typically a spontaneous regression without any intervention, help to clinically distinguish this entity.

Between 4 and 10% of newborn infants with DS are thought to develop TMD. Until recently, most attempts to describe this unique leukemia have come from single institutions or surveys. Derived from these early reports and more recently registries was that in addition to its typical spontaneous regression within 3-7 months of life without intervention it appeared to have a highly fatal form, and among those who survived there was up to a 20 to 30% risk of subsequent leukemia.

The Children’s Oncology Group (COG) A2971 study, reported here, is the largest study to date designed to define the natural history of clinically diagnosed TMD utilizing prospectively uniform observation and treatment guidelines. To achieve this goal, this study for the first time identified infants with TMD utilizing uniform 1) clinical diagnostic criteria, 2) intervention guidelines where needed, and 3) monitoring guidelines...
after resolution of the TMD for physicians to follow. This trial, while not a population prevalence study, sought to better describe the breadth of clinical TMD presentations, and among those clinically diagnosed with TMD (i.e., without the use of GATA1 mutation analysis), its natural course towards spontaneous remission, its complication and case-fatality rates, and the subsequent risk of acute leukemia later in early childhood. DS children who later developed AML and those who developed AML without a known history of prior TMD were treated on a separate arm of this study and are reported separately.

Patients, materials, and methods

Eligible patients (n=135) with TMD were enrolled between 1999 and 2004 from participating COG institutions (n=115) with institutional IRB approvals for COG A2971. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed by the ethics committee or institutional review board at each participating center. All patients’ parents gave written informed consent, according to institutional regulations, prior to enrollment and chemotherapy administration.

Broad eligibility criteria were utilized within this study to capture the full spectrum of clinical TMD. Children were eligible if found to have trisomy 21 as a constitutional finding, a mosaic distribution, or as a finding limited to the hematopoietic or leukemic cells. Diagnosis and eligibility were made if they were <3 months of age at presentation with any non-erythroid blasts in the peripheral blood coupled with any of the five following criteria: verification of blasts with a second sample, >5% non-erythroid bone marrow blasts, hepatomegaly or splenomegaly, lymphadenopathy, or cardiac or pleural effusions. Non-standardized institutional complete blood counts (CBC) were used and correction for nucleated RBC was not defined in this trial. Organomegaly or adenopathy were determined by the clinician’s physical exam and did not have strict criteria to make these diagnoses. Down syndrome infants without peripheral blasts were also eligible if they had biopsy proven or cytology proven blasts in an affected organ, or in sampled fluid (pericardial, pleural, or peritoneal). A marrow aspirate was advised but not required at the time of enrollment and depended upon the patient’s condition and family’s consent. This trial began prior to reports of an association between GATA1 and TMD and did not collect banked leukemia samples to determine mutation prevalence in this trial.

Most patients were referred to a COG center and seen while still with TMD though a small percentage of patients (1.5%) were enrolled after the TMD had resolved. Patients were enrolled within 14 days of diagnosis by a hematologist or within 72 hours of starting chemotherapy if used.

Patients were seen at specified frequencies until TMD resolution, as well as subsequently to the time to development of AML, or for a period of 5 years to determine leukemia-free survival (LFS) (see Supplemental Table A). Patients were enrolled to either observation or intervention arms of the study based on severity of presenting signs and symptoms. The majority of patients (72%) had no life threatening symptoms at any time and were
observed. Life-threatening symptoms (LTS), the sole criteria for intervention, were prospectively defined by one or more of the following: signs of hyperviscosity, blast count >100,000/µL, hepatosplenomegaly causing respiratory compromise, heart failure (EF <47% or SF <27%) not directly due to a congenital heart defect, hydrops fetalis, renal or hepatic dysfunction, or DIC with bleeding. Criteria without a specific exceeded value were based upon the judgment of the physician. The goal of intervention was to reduce symptoms to tolerable levels (defined by the treating physician) as spontaneous resolution was expected.

Most patients with LTS (N=29/38) due to high WBC counts were treated with exchange transfusion or leukapheresis (ExT/L) or chemotherapy consisting of continuous infusion cytarabine at 3.33 mg/kg/24hours for 5 days. Patients with significant organ compromise were treated with chemotherapy that could be repeated every 14 days after count recovery for no more than 3 courses. Exchange transfusions and/or leukapheresis had no minimum interval between procedures. Patients who failed to resolve LTS, after these interventions and prior to TMD remission, were to be transferred to the AML arm of this study (n=0). Once LTS resolved with intervention no longer required, patients were seen at set frequencies similar to those not requiring intervention (see Supplemental table A). Patients initially observed were permitted to later receive intervention as needed if they were <90 days of age (n=2).

Complete remission (CR) of TMD was defined as resolution of peripheral blasts, evidence of trilineage recovery, disappearance of effusions, and organomegaly resolution on two consecutive occasions >7 days apart. Hematologic CR was assessed to adjust for the hepatic fibrosis known to persist after peripheral blast resolution and count recovery in many patients and did not require the resolution of hepatomegaly. Marrow remission determination was not required for either definition. Patients in CR >8 weeks, older than 90 days, and who had ≥30% marrow blasts (based upon FAB AML criteria) were to be diagnosed with AML and treated appropriately for DS AML. Patients who were older than 90 days and who had ≥5% marrow blasts in the presence of myelodysplasia were to be diagnosed to have MDS and treated similarly to those diagnosed with AML.

Statistical analysis

At the time of this report, the study was current as of July 7, 2008. The significance of observed differences in proportions was tested using the Chi-squared test and Fisher’s exact test when data were sparse. The Mann-Whitney test was used to determine the significance between differences in medians. The Kaplan-Meier method was used to calculate estimates of overall survival (OS), event-free survival (EFS) and TMD-related mortality. Estimates are reported with their Greenwood standard errors. Differences in these estimates were tested for significance using the log-rank statistic\(^\text{13}\). OS was defined as time from study entry until death. EFS was defined as time to TMD recurrence, death or development of either AML, MDS or Acute lymphoblastic leukemia (ALL). TMD related mortality was defined as time to death related to TMD where deaths unrelated to TMD and patients who developed AML/ALL/MDS were censored. Modified EFS
(mEFS) and LFS were estimated by methods of competing risks\textsuperscript{14}. Modified EFS was defined similarly to the above definition of EFS except that patients having non-TMD related deaths were classified as competing events. LFS is defined as time from resolution to development of AML/ALL/MDS where patients who died prior to development were considered competing events. Gray’s p-value was used to compare groups of patients for modified EFS and LFS analyses. Children lost to follow-up were censored at their date of last known contact or at a cutoff 6 months prior to July 7, 2008. Cox regression models were also used for univariate and multivariate analyses comparing differences between characteristic groups defined by WBC count, BM blasts, platelets, hepatomegaly, splenomegaly or other characteristics taken from the time of diagnosis\textsuperscript{15}.

Results

Patient Characteristics

There were 139 patients enrolled from 1999-2004 of whom 4 were ineligible (either receiving treatment and not having a marrow exam performed prior to enrollment, having AML and not TMD, or having an incomplete registration) leaving 135 analyzed patients with a median follow-up of 1153 days (0-2857) from diagnosis. Presenting characteristics and intervention assignment are listed in Table 1 and the Supplemental Table B. Most presented within the first week of life. Trisomy 21 was confirmed in all eligible DS patients with mosaicism for trisomy 21 found in 16% of these. Most were full-term (67%) though those in need of intervention were more frequently premature (50%). Congenital anomalies other than trisomy 21 phenotypic stigmata were found in 68% of children. Congenital cardiac or GI abnormalities (including duodenal atresia) were seen most often, 57% and 10%, respectively, with no significant difference between those needing intervention and those not. Median WBC at diagnosis was elevated whereas hemoglobin was generally normal and platelets were only slightly reduced (7/135 were <150,000/µl). Peripheral blast percentage equaled or exceeded the marrow blast percentage in 69% of patients with marrow exams (74/107). Sixteen (12%) children had an initial WBC >100,000/µl, however only 11 received treatment. Hepatomegaly (HM) was the most prevalent symptom of organ infiltration present in 58%. Pericardial effusions and congestive heart failure (CHF) were more likely to occur in those with underlying cardiac defects vs. those without cardiac defects (effusion: 16% vs. 2%; CHF: 8% vs. 2%). Patients were assigned by their clinicians to observation (n=106) or intervention (n=29) arms based upon the prospectively designated clinical severity criteria detailed above. Among the 108 initially observed, 2 later had LTS and required intervention, and 9 others had at least one LTS at diagnosis but were not treated (5 due to resolving symptoms at enrollment, 2 where the clinician chose not to intervene, 1 where the LTS were felt to be due to co-existing biliary atresia, and 1 in which AML therapy was utilized rather than TMD – see below).

Patients Requiring Intervention

Those with LTS (n=38) and in whom the treating physician elected to pursue intervention (n=29) constituted 22% of the TMD patients. Patients required intervention due to
hyperviscosity (11%), blast count >100,000/µl (25%), organomegaly (OM) with respiratory compromise (43%), CHF (11%), hydrops fetalis (21%), liver dysfunction (43%), renal dysfunction (14%), or DIC (25%). All with symptoms of hyperviscosity, CHF not due to congenital heart defects, and renal dysfunction did go on to an intervention. Among the other symptoms that could trigger intervention, 69% (11/16) with WBC >100,000/µl, 92% (12/13) with respiratory compromise due to OM, 75% (6/8) with hydrops fetalis, 71% (12/17) with hepatic dysfunction, and 88% (7/8) with DIC received therapy. Those receiving intervention for symptoms that define life-threatening disease were significantly younger at diagnosis, more likely to be premature, and found with a lower hemoglobin at diagnosis. Mosaic DS children were as likely to require intervention as fully constitutional DS children (14% vs. 23%, p=0.407). Among the intervention patients, most had complete trisomy of chromosome 21 (n=26) rather than mosaic trisomy 21 (n=3). Nine (31%) received ExT/L and 24 (83%) received low-dose cytarabine for OM, organ dysfunction causing respiratory compromise, or continued symptoms after ExT/L. Four children required subsequent cytarabine after initial management with ExT/L. Two additional patients at 5 and 39 days after diagnosis (9 & 54 days of life, respectively) required transfer from the observation arm to the intervention arm when LTS first arose after diagnosis (ExT/L, n=1; ExT/L and cytarabine, n=1), both of whom survived the episode and required no further therapy for their TMD.

Among patients receiving ExT/L (n=10), the TMD was controlled sufficiently in two patients to avoid further intervention; two died after receiving 1 course of intervention. Six required further intervention for severe TMD symptoms: one received a second course (ExT/L) and five subsequently were given cytarabine. Among those 24 receiving cytarabine, only one received an additional course for ongoing LTS as determined by the treating physician. Among the 24 patients requiring cytarabine, 96% had at least one grade 3 or 4 toxicity which was most frequently myelosuppression (anemia, 38% (n = 9), leucopenia, 58% (n = 14), or thrombocytopenia, 83% (n = 20)). Ultimately, 15 were able to be followed without further intervention whereas 13 succumbed to their TMD or treatment related complications, and one died due to complications unrelated to their TMD. No patient transferred to the other arm of the trial for traditional AML therapy in order to specifically further treat their TMD. Several ultimately were treated for later occurrences of AML and are discussed below.

Patients Not Requiring Intervention

Of 108 observation arm patients, 106 achieved a spontaneous remission and 2 were transferred to the intervention arm due to delayed LTS occurrence (described above). Median time to TMD resolution from diagnosis was 49 days (range 5-745 days) (Figure 1; Supplemental Table C). Peripheral blast resolution was attained in a median of 36 days (range 2-126 days). The difference, particularly in those in whom resolution of TMD was quite prolonged (>180 days, n=7), was entirely due to prolonged hepatomegaly. The time for peripheral blast resolution was decreased among those receiving intervention, whereas there was no impact upon organomegaly resolution with intervention.
Outcomes and Prognostic Factors

Among all 135 patients (Table 2), the 3-year OS was 77 ± 8% (±2 standard deviation), EFS was 57 ± 10%, and mEFS was 68 ± 9% (Figures 2 & 3). Twenty-nine deaths were recorded (14 related, 14 unrelated to TMD or therapy, 1 unknown). There was an overall case-fatality rate (death due to TMD) of 10% whereas total mortality was 21%. Of 14 deaths in the intervention arm patients, 13 were determined to be TMD related. Of 15 deaths in the observation arm patients, only 1 patient had unresolved TMD at the time of death. This patient was initially observed despite a white count of 135,000, and when progressive hepatic dysfunction developed, the physician chose to treat off study with this trial’s AML therapy. This infant died due to neutropenic \textit{Staphylococcus epidermidis} sepsis complicated by massive ascites and hepatic dysfunction. As such, there was a significantly greater case-fatality rate in the intervention group (13/29, 45%) as compared to those not requiring intervention (1/106, 1%).

Examination of clinical characteristics at the time of TMD diagnosis were evaluated by univariate Cox analysis for their impact upon OS, EFS, and mEFS (Supplemental Table D). For OS, hepatomegaly (Hazards Ratio-HR 3.06, p=0.015), hyperleukocytosis (defined as >100,000 WBC/µl) (HR 3.25, p=0.007), and black (and non-white) race (HR 4.36, p=0.003 for black vs. not black and HR 2.46, p=0.024 for white vs. not white) were associated with increased overall mortality. Hepatomegaly (Figure 4a) and hyperleukocytosis (Figure 4b) among these three factors had a significant or near-significant impact upon mEFS (survival until the time of TMD remission). Finally, when considering all events before and after TMD resolution, EFS was significantly impacted by all three risk factors. These risk factors for these survival analyses (OS, EFS, and mEFS) maintained or trended towards significance in multivariate modeling (Supplemental Table E). Platelet count, peripheral compared to marrow blast percentage, gestational age, splenomegaly, cardiac lesion, congenital anomaly or Trisomy 21 mosaicism did not impact survival in univariate Cox analyses.

As patients with severe TMD were guided to intervention, a further comparison of symptoms and signs between the patients receiving intervention who died and those who did not was pursued. Only age at diagnosis (median 1 day of age among those dying vs. 6 days of age among surviving, p=0.013) and the presence of renal dysfunction at diagnosis (found in 31% of those who later died v 0% among those who survived, p=0.035) reached statistical significance for mortality risk. White blood count >100,000/µl (39 vs. 13%, p=.198), elevated ALT (77% v 40%, p=.067), and congenital heart disease (100% vs. 71%, p=0.137) were more prevalent among those who died but did not achieve statistical significance. Whereas black race was a univariate prognostic factor among all causes of mortality, when restricted to the intervention patients of whom all but two died of TMD-related causes, it was no longer prognostic (p=0.583). Also gestational age, CHF, organomegaly causing respiratory compromise, median WBC, or bilirubin or hepatic dysfunction failed to exhibit differences between those who died and lived after or during intervention.

Categorizing Survival based upon hepatomegaly and/or LTS presence
A survival risk classification was developed to identify children in need of intervention at diagnosis, particularly due to the high prevalence of hepatomegaly. Dividing patients into three risk groups (Table 3) resulted in classifying TMD patients as “low risk” if they had no evidence of LTS nor hepatomegaly and thus no need for intervention (n = 51, 38%), “intermediate risk” if they had any degree of hepatomegaly with or without hepatic dysfunction but not determined to be severe enough to require intervention (n=55, 41%); and “high risk” if they presented with LTS from cardio-respiratory compromise, hepatic dysfunction, or hyperleukocytosis requiring intervention (n = 29, 21%). The OS for low, intermediate and high risk groups was 92±8%, 77±12% and 51±19% and mEFS (Figure 5) was 78±14%, 75±13% and 36±18%, respectively (p<0.001 for low vs. high, and intermediate vs. high risk groups for OS and mEFS). The 3-year LFS among those who attained TMD CR was 79±15%, 77±14%, and 71±25% respectively.

Subsequent AML/MDS risk

Once TMD had resolved, patients were systematically seen at a set frequency to monitor for the recurrence of TMD as well as later acute leukemia. To date, 21 patients (16%), including 4 prior intervention patients of whom 3 received cytarabine, have developed AML/MDS at a median time of 441 days (range 118-1085 days) (Table 1). There was no significant difference in incidence of subsequent AML between those receiving cytarabine (3/24, 13%) vs. those not (18/111, 16%) (p=0.766). Among all clinical factors at diagnosis or during the clinical course, only time to TMD resolution approached a significant correlation with the risk of later development of AML. Dividing the patients into two groups depending on whether their TMD resolved sooner or later than the median (47 days from diagnosis) found that those with TMD resolution shorter or equal to the median time had a 3 yr LFS of 82+14 % compared to 71 + 13% (p=0.063) for those with longer resolution times. Additionally, two patients developed acute lymphoblastic leukemia at 727 and 851 days of life.

Discussion

This prospective trial for children with DS clinically diagnosed with TMD has been able to ascertain the natural history of a heretofore enigmatic disorder that despite its well-known and unique characteristic of spontaneous resolution, was also considered to have a relatively high risk of mortality before it resolved. Additionally, based upon this mortality risk this trial provided guidelines for intervention and utilized a moderately low dose of cytarabine in order to control the myeloproliferation, if life-threatening, until spontaneous regression began. By establishing these prospective monitoring and intervention guidelines, a natural history among those clinically diagnosed with TMD with less confounding variability is elucidated.

In previous case series, TMD was found to have a high case fatality rate, despite the generally accepted approach of supportive care until the disease’s spontaneous resolution. This has led to significant confusion and unease among clinicians as to the proper route of action when a patient with TMD presents. In this trial, 78% of children with TMD had
mild symptoms and spontaneous resolution of their disease without intervention, similar
to a recent report from the BFM (84%)\(^{16}\). This ranged from those who only had transient
blasts in the peripheral blood (31%) to those with mild organomegaly such as
hepatomegaly (58%), abnormal liver function studies (41%), and splenomegaly (36%),
similar to other recent reports\(^{11,16}\).

In comparison, those patients who presented in moribund condition or with LTS were
likely to lead to mortality if intervention is not implemented. Organ infiltration,
primarily hepatic, may be severe, progressive, and fatal\(^{9,17,18}\). Hayashi et al. found 10 of
15 TMD patients died within the first few months of DIC, hepatic failure, or renal
failure\(^9\). Zipursky et al. identified 7 of 13 severe TMD patients in the literature died, of
whom 5 were stillborn, and 2 died later\(^{17}\). Hydrops fetalis was a predominant symptom
in these patients with prominent blast infiltration of the heart and liver found at autopsy
with associated fibrosis whereas none of these findings were found in the marrow\(^{17}\).
Three of the 4 reviewed patients died within 24 hours of birth. Subsequently, Al-Kasim
et al.\(^{18}\) further described the central role of hepatic involvement in those with a fatal
outcome. Nine of 48 patients enrolled had life-threatening disease, 7 with hepatic
fibrosis and 2 with cardiorespiratory failure. Without intervention all died, whereas 3
children in whom short courses of low dose cytarabine were administered survived.
More recently, Klusmann et al.\(^{16}\) reported the BFM registry experience which identified
high risk patients (high WBC, prematurity, ascites, and failure of TMD resolution) had an
improved outcome if intervention was given (72 vs. 24%, \(p=0.001\)). Intervention clearly
appears to have a role in supporting these children through a critical period of their
disease.

As seen in the prior two reports, where hepatic fibrosis was pathologically diagnosed all
have died. Whether hepatomegaly alone is a criterion for intervention is a frequently
asked question among clinicians. It was a prominent feature in this (58%) and other
trials, and is presumably the site of TMD origin\(^{11,16}\). However, it alone does not portend
a high mortality risk as it was equally present in both those who required intervention or
did not require (48% and 46%, respectively). In those in whom LTS were present, as
pre-defined by the protocol for intervention, massive hepatomegaly (i.e., below the
umbilicus) was more often present and presumed to be one of the primary causes of these
symptoms. This association with other LTS was found in 24% of enrolled patients. In
this intervention group, massive hepatic enlargement was seen in 38% compared to only
4% in the cohort who did not meet the threshold for intervention. In this trial, hepatic
complications of TMD were apparent in all children at the time of death who died of
TMD-related causes except one who died of hydrops-induced multi-organ failure.

Because of this wide range of presentations and their incumbent mortality risks, it is
important to better ascertain who may or may not require intervention prior to
spontaneous resolution. This study proposes a mortality risk-based classification system
to stratify the treatment of TMD patients. We identified three distinct TMD risk groups.
High risk patients have early evidence of LTS and a TMD-associated mortality rate of
55% at 3 years. Most infants with TMD (41%) belong to the intermediate risk group,
specifically those with hepatomegaly though without LTS. These infants rarely die from
acute complications of TMD; however, they have a 23% 3 year mortality rate. Deaths were due to congenital heart defects (n=5), SIDS-like events (n=2), tracheal stenosis (n=1), subsequent AML & relapse (n=1), and for unknown reasons outside the country (n=1). This is double the overall mortality rate of the low risk group and is disproportionately higher than the mortality rates of DS infants without TMD\textsuperscript{19,20,21,22}. The rest (38%) are the classic “low risk” patients that spontaneously resolve their disease without therapeutic intervention. Low risk patients have less than a 2.3% chance of dying from acute complications of TMD.

Overall mortality in our population was 21.5% consistent with reports of 16-23% in the literature\textsuperscript{11,17}. However, TMD related mortality was 11% as most deaths were non-TMD related in this cohort of children known to have a significant incidence of other life-threatening congenital anomalies. For those with LTS, there is a high case-fatality rate (45%).

The most appropriate dose, administration, and scheduling of low dose cytarabine for TMD patients is unknown. In this study, those with LTS were treated with continuous infusion cytarabine (CI cytarabine) at 3.33 mg/kg/24 hours over five days, similar to the protocol’s AML induction dose. Virtually all (23/24, 96%) cytarabine treated patients experienced Grade 3/4 myelosuppression. All deaths among those requiring cytarabine were related to TMD and its sequelae, although prolonged neutropenia may have contributed to the poor outcome of those who died of infectious complications. Only one of the 24 infants who required cytarabine received more than one course. Despite additional intervention this infant succumbed from TMD-associated complications. This suggests that lower doses of cytarabine with less significant hematologic toxicity need to be investigated. The use of lower subcutaneous cytarabine dosing (0.5-1.5 mg/kg) for 3-12 days has been reported\textsuperscript{11,16,18}.

A better understanding of the natural history of clinically diagnosed TMD is derived from this trial and provides a clearer understanding as clinicians compare their own patients to the full spectrum of TMD patients. All patients resolved their TMD by 745 days with a median time to resolution of 47 days (range 5-745 days). Peripheral blasts cleared at an earlier median of 33 days (range 2-126 days) than hepatomegaly resolution (45.5 days, range 0 -745 days).

While time to complete resolution is of interest, the greatest concerns are two-fold. Which patients may still develop LTS in whom intervention is needed, and which may truly be a child with AML that does not spontaneously resolve? Only two patients initially felt not to have LTS subsequently required intervention. The reasons for both were rising peripheral blast counts that eventually exceeded 100,000. Intervention occurred on days 5 and 39 from diagnosis (or 9 and 54 days from birth), respectively. Thus, beyond 39 days from diagnosis, no patient subsequently required intervention.

As intervention may have confounded the determination of who did and did not have true AML, one must examine other characteristics (other than age) felt to distinguish AML from TMD in the DS population. As has been recognized previously, hepatic
involvement has been more often seen in TMD than in AML patients in whom marrow involvement is more prevalent. Examination in those in whom a marrow exam was performed at the time of their TMD diagnosis showed 31% (33/107) had more blasts in the marrow than in the periphery. Within the observation group who did not receive intervention, this degree of marrow involvement was not associated with failure to eventually resolve their TMD nor was it associated with later development of AML (3 yr OS, marrow blasts > PB blasts, 79±13% vs. 79±11%, p=0.875; 3 yr EFS, 57±17% vs. 63±13% respectively, p=0.711).

Later development of AML is known to occur in TMD patients. Zipursky et al. first in a literature review and later in a survey identified 26-30% went on to develop leukemia in the first 3 years of life 8, 23. More recently the POG and the BFM cooperative groups identified 19-23% later developed acute leukemia, primarily myeloid 11, 16. To date, 21 patients among the 135 enrolled (16%), including 4 treated with cytarabine, developed AML/MDS at a median time of 441 days (118-1085). Among those who achieved TMD remission, the 3 year cumulative incidence of subsequent AML was 20 ± 9% from remission and among those surviving to age 6 months, 21/111 (18.9%) later developed AML. Examining risk factors for later AML development, only the time to resolution was predictive. Using the median time to resolution of 47 days from diagnosis for the entire cohort, those that took <47 days to TMD resolution had a better 3 year LFS (82% vs. 71%). Can the early use of chemotherapy in TMD prevent later occurrence of AML? This was not found to be beneficial in our group as four of 24 (17%) cytarabine recipients later developed AML, comparable to 14 of 111 (13%) who did not receive chemotherapy for TMD (p=0.527). This was similarly found in the BFM study (27 and 23% (p=.46), respectively)16.

This study is not a population-based study and thus the incidence of TMD within DS patients cannot be directly ascertained. There is likely a group of children with DS with milder manifestations of TMD that goes undiagnosed prior to its spontaneous resolution. Analysis of 590 Guthrie cards from infants with DS born in New York State revealed a GATA1 mutation incidence of 3.8% (22/585 evaluable)24. Nevertheless, this study sought to examine the full range of patients with TMD who are diagnosed either due to TMD related symptoms or serendipitously during other exams in the newborn and infant period. As such, this trial prospectively defined TMD to include all potential patients as long as there were verified blasts on two separate examinations or symptoms or signs of TMD in addition to the identification of blasts on a single laboratory exam. As this trial was designed prior to the discovery of the GATA1 association and did not determine the presence of this mutation (nor were there banked specimens to retrospectively determine this), it is possible that some of the most mild presentations of TMD in our cohort may have simply represented a leukemoid reaction. However, only 8 of the patients in whom this might be considered were found with the most minimal of symptoms (e.g., transient peripheral blasts alone that cleared within 7 days). Nevertheless, in this way, this study likely represents the full spectrum of TMD manifestations even though an incidence cannot be derived from this analysis.
This portion of the COG trial, A2971, further clarifies the natural history of clinically diagnosed TMD, identifies risk groups for survival and development of subsequent AML, and provides baseline comparisons for upcoming COG and other trials of TMD. A current COG trial, AAML08B1, is focusing upon the biological characteristics of TMD including molecular mutations such as GATA-1 known to occur in the vast majority if not all TMD patients, the correlates with acute morbidity, particularly fibrosis, as well as the biologic analyses in each patient who both has TMD and later develops AML.

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Author contributions:
A Gamis: Designed research, performed research, analyzed and interpreted data, wrote the manuscript.
T Alonzo: Designed research, performed research, analyzed and interpreted data, performed statistical analysis, edited manuscript.
R Gerbing: Analyzed and interpreted data, performed statistical analysis, edited manuscript.
J Hilden: Designed research, performed research, edited manuscript.
A Sorrell: Performed research, edited manuscript.
M Kumar: Analyzed and interpreted data, edited manuscript.
T Loew: Performed research, edited manuscript.
R Arceci: Performed research, edited manuscript.
D Barnard: Performed research, edited manuscript.
J Doyle: Performed research, edited manuscript.
G Massey: Performed research, edited manuscript.
J Perentesis: Performed research, edited manuscript.
Y Ravindranath: Performed research, edited manuscript.
J Taub: Performed research, edited manuscript.
F Smith: Designed research, performed research, edited manuscript.

The authors have no disclosures to report.
### Table 1: Selected TMD patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>All TMD patients</th>
<th>TMD: Observation only</th>
<th>TMD: Intervention</th>
<th>Observation vs Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>Median (Range)</td>
<td>N</td>
</tr>
<tr>
<td>Total enrolled</td>
<td>130</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># ineligible</td>
<td>4</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td># eligible</td>
<td>135</td>
<td>97%</td>
<td>106 (78.5%)</td>
<td>29</td>
</tr>
<tr>
<td>Treatment arm at time of registration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation</td>
<td>106</td>
<td>80.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received TMD intervention later</td>
<td>2</td>
<td>1.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopheresis/Exchange transfusion</td>
<td>5</td>
<td>3.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy (All-1)</td>
<td>22</td>
<td>16.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (days)</td>
<td>5</td>
<td></td>
<td>(0 - 58)</td>
<td></td>
</tr>
<tr>
<td>Age at study entry (days)</td>
<td>13</td>
<td></td>
<td>(1 - 66)</td>
<td></td>
</tr>
<tr>
<td>Follow-up time (days)</td>
<td>1153</td>
<td>1196</td>
<td>(6-3257)</td>
<td></td>
</tr>
<tr>
<td>Time to development of AML/MDS (days)</td>
<td>21</td>
<td></td>
<td>441 (118-1005)</td>
<td>17</td>
</tr>
<tr>
<td>Constitutional trisomy 21</td>
<td>113</td>
<td>83.7%</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Trisomy 21 mosaicism</td>
<td>22</td>
<td>16.3%</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>57</td>
<td>42.2%</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Enlarged but not below umbilicus</td>
<td>63</td>
<td>46.7%</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Below umbilicus</td>
<td>15</td>
<td>11.1%</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Liver dysfunction (symptomatic)</td>
<td>17</td>
<td>12.7%</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Unknown</td>
<td>17</td>
<td>12.7%</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Organomegaly (liver or spleen) with</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>respiratory compromise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>9.7%</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>No</td>
<td>121</td>
<td>90.3%</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>0.8%</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Diagnostic Laboratory Exam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (x 10^9/μL)</td>
<td>32.0</td>
<td>(4.8-259)</td>
<td></td>
<td>26.0</td>
</tr>
<tr>
<td>A total blast count of ≥100,000/μL</td>
<td>6</td>
<td>11.5%</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Yes</td>
<td>25</td>
<td>9.3%</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Blasts in peripheral blood (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Marrow Blasts (%)</td>
<td>14</td>
<td>(6.95)</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>HGB (gm/dL)</td>
<td>11.9</td>
<td>(5.0-22.5)</td>
<td></td>
<td>15.6</td>
</tr>
<tr>
<td>Platelet count (x 10^9/μL)</td>
<td>112</td>
<td>(10-958)</td>
<td></td>
<td>112</td>
</tr>
</tbody>
</table>
Table 2: TMD Outcomes

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Observation patients</th>
<th>Intervention patients</th>
<th>Observation vs Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>3 year %</td>
<td>±2 SE%</td>
<td>N</td>
</tr>
<tr>
<td>OS from study entry</td>
<td>135</td>
<td>77% ± 6%</td>
<td></td>
<td>106</td>
</tr>
<tr>
<td>EFS from study entry</td>
<td>135</td>
<td>57% ± 10%</td>
<td></td>
<td>106</td>
</tr>
<tr>
<td>mEFS from study entry</td>
<td>135</td>
<td>68% ± 9%</td>
<td></td>
<td>106</td>
</tr>
<tr>
<td>LFS from resolution for patients who resolve their TMD</td>
<td>107</td>
<td>80% ± 9%</td>
<td></td>
<td>92</td>
</tr>
</tbody>
</table>

Table 3: Outcome by risk groups

<table>
<thead>
<tr>
<th></th>
<th>Risk Group</th>
<th>log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Event free survival - year 3 estimate*</td>
<td>51</td>
<td>55</td>
</tr>
<tr>
<td>Overall survival - year 3 estimate*</td>
<td>92.1 ± 8%</td>
<td>77.2 ± 12%</td>
</tr>
<tr>
<td>TMD related mortality - year 3 estimate*</td>
<td>2 ± 4%</td>
<td>0 ± 0%</td>
</tr>
</tbody>
</table>

*development of AML is considered an event

Figure 1: Time to TMD Resolution from diagnosis for all patients enrolled.

Figure 2: OS and EFS from study entry for all TMD patients.

Figure 3: OS and modified EFS from study entry comparing observation to intervention patients. Deaths that are not TMD related are competing events in modified EFS (1 - Cumulative Incidence).

Figure 4a & b: Hepatomegaly and hyperleukocytosis impact upon OS & modified EFS.

Figure 5: OS & modified EFS for the 3 risk groups of TMD patients. This illustrates that the intermediate risk group, i.e. those with hepatomegaly alone, had minimal TMD related problems but did have significant mortality from other causes.

Figure 6: Leukemia-free survival from time of TMD resolution comparing those children whose TMD resolved at or sooner than the median time to resolution (47 days) versus those whose time to TMD resolution took longer.
Figure 1

Figure 2
Figure 3

Figure 4a
Figure 4b

![Graph showing Survival vs Years from study entry for different WBC categories and mEFS categories.]

Figure 5

![Graph showing Probability vs Years from study entry for different OS and mEFS risk categories.]

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Figure 6
References


Natural history of transient myeloproliferative disorder clinically diagnosed in Down syndrome neonates: a report from the Children's Oncology Group Study A2971

Alan S Gamis, Todd A Alonzo, Robert B Gerbing, Joanne M Hilden, April D Sorrell, Mukta Sharma, Thomas W Loew, Robert J Arceci, Dorothy Barnard, John Doyle, Gita Massey, John Perentesis, Yaddanapudi Ravindranath, Jeffrey Taub and Franklin O Smith

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