Transient Myeloproliferative Disorder

HEMATOLOGY ONCOLOGY DEPARTMENT

Background

- Unique syndrome common to infants with Down syndrome-may affect up to 20%
- Historically called transient abnormal myelopoiesis or transient leukemia.
- No current recommendation for screening.

Etiology

- Still not completely known, BUT disease is restricted to patients with trisomy 21
- Gene dose-possibility that trisomy is “first hit”
  - FPDMM gene
  - AML1 gene
  - IFN-alpha-beta gene
- In addition, mutations in the exon of 2 of the GATA-1 gene have detected exclusively in patients with Down syndrome and either TMD or AMKL…

GATA-1 mutation

- GATA-1 is a gene on the X chromosome that encodes for a transcription factor
- This transcription factor is necessary for normal proliferation and differentiation of megakaryocytes and erythroid cells, eosinophils and mast cells
- Mutations in GATA-1 are seen with TMD and DS associated AMKL
- Other non DS patients with AMKL do not display GATA-1 mutations
- DS patient with other types of leukemia do not display GATA-1 mutations

Blood 2004; 103:399-406

Clinical and laboratory features

- Can be asymptomatic finding or associated with severe clinical disease
- Enlargement of the liver and spleen
- Blasts in the blood, but a lesser degree of bone marrow infiltration
- Morphologically, **cytochemically and on immunophenotyping the blast cells resemble those of acute megakaryoblastic leukemia**
- Most regress spontaneously without treatment

Pediatric Blood Cancer 2005; 44:40-44

Clinical and laboratory features

- In severe cases, patients can present with:
  - Hydrops fetalis prenatally/postnatally
  - High levels of circulating blasts
  - Hepatomegaly from hepatic fibrosis-associated with increased bilirubin, LFT's, coagulopathy
  - Pericardial or pleural effusion, ascites
  - Multisystem organ failure

A prospective study of the natural history of transient leukemia (TL) in neonates with Down syndrome (DS): Children's Oncology Group (COG) study POG-9481

Gita V. Massey, Alvin Zipursky, Myron N. Chang, John J. Doyle, Suhail Nasim, Jeffrey W. Taub, Yaddanapudi Ravindranath, Gary Dahl, and Howard J. Weinstein

A unique transient leukemia (TL) has been described in newborns with Down syndrome (DS; or trisomy 21 mosaics). This leukemia has a high incidence of spontaneous remission; however, early death and subsequent development of acute megakaryoblastic leukemia (AMKL) have been reported. We prospectively evaluated 48 infants with DS and TL to determine the natural history and biologic characteristics of this disease, identify the clinical characteristics associated with early death or subsequent leukemia, and assess the incidence of subsequent leukemia. Blast cells associated with TL in DS infants exhibited FAB M_7 morphology and phenotype. Most infants (74%) had trisomy 21 (or mosaicism) as the only cytogenetic abnormality in the blast cells. Most children were able to spontaneously clear peripheral blasts (89%), normalize blood counts (74%), and maintain a complete remission (64%). Early death occurred in 17% of infants and was significantly correlated with higher white blood cell count at diagnosis ($P < .001$), increased bilirubin and liver enzymes ($P < .005$), and a failure to normalize the blood count ($P = .001$). Recurrence of leukemia occurred in 19% of infants at a mean of 20 months. Development of leukemia was significantly correlated with karyotypic abnormalities in addition to trisomy 21 ($P = .037$). Ongoing collaborative clinical studies are needed to determine the optimal role of chemotherapy for infants at risk for increased mortality or disease recurrence and to further the knowledge of the unique biologic features of this TL. (Blood. 2006; 107:4606-4613)

POG 9481 study

- POG 9481 was initiated in 1996 to prospectively study biology and clinical features of TMD
- 48 patients with DS were enrolled
- All had evidence of TMD (circulating blasts, blast in effusion or solid organ)
- 60% male, 40% female
- Mean age at diagnosis was 13 days (1-65 days)

POG 9481 study

- 75% of patients were symptomatic at diagnosis

Table 1. Symptoms at presentation of TL in 48 patients

Clinical symptoms	Prevalence, no. (%)
Asymptomatic*	12 (25)
Symptomatic	36 (75)
Abdominal distention	13 (27)
Bruising/petechiae/bleeding	12 (25)
Respiratory distress (hypoxia, apnea, tachypnea)	10 (21)
Jaundice	6 (13)
Rash (not petechial)	5 (10)
Heart murmur/CHF	5 (10)
Failure to thrive/IUGR	5 (10)
Vomiting/diarrhea	2 (4)
Pallor	1 (2)
Hypoglycemia	1 (2)
Hypothermia	1 (2)
Infection	1 (2)

CHF indicates congestive heart failure; IUGR, intrauterine growth retardation.
*Abnormal blood counts or blasts on peripheral smear only.

POG 9481 study

- 42/47 patients had disappearance of peripheral blast within a mean of 58 days (2-194 days)
- 35/42 children above normalized their blood counts within a mean of 84 days (2-201 days)
- The other 7 children went on to early death (n=3) or developed leukemia (n=4)

POG 9481 study

- 30/47 children remain in remisson, with normal blood counts and no evidence of leukemia.
- 9/47 children subsequently developed leukemia at a mean age of 20 months (19%)
- 8/47 children died at less than 9 months of age.
  - All who died had liver failure and disseminated intravascular coagulopathy as terminal events.

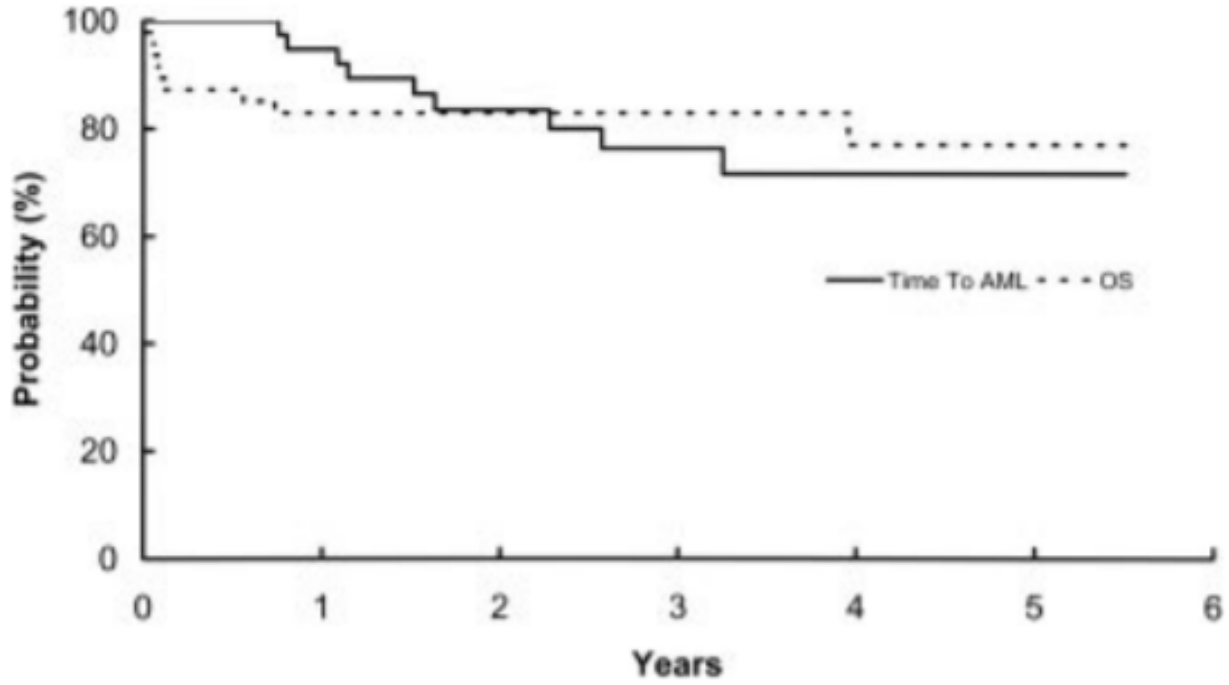

Figure 2. Kaplan-Meier curves show the time to development of leukemia and overall survival. Time to leukemia represents the probability of remaining free of leukemia. OS indicates overall survival.

CME article

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,[1] Todd A. Alonzo,[2] Robert B. Gerbing,[3] Joanne M. Hilden,[4] April D. Sorrell,[5] Mukta Sharma,[1] Thomas W. Loew,[6] Robert J. Arceci,[7] Dorothy Barnard,[8] John Doyle,[9] Gita Massey,[10] John Perentesis,[11] Yaddanapudi Ravindranath,[12] Jeffrey Taub,[12] and Franklin O. Smith[11]

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

COG A2971

- Eligible patients n= 135
- Patients < 3 months with blast in peripheral blood AND any of 5 following criteria
  - Verification of blasts with a second sample
  - >5% nonerythroid bone marrow blasts
  - Hepatomegaly or splenomegaly
  - Lymphadenopathy
  - Cardiac or pleural effusion

COG A2971

- Criteria for intervention
  - Signs of hyperviscosity
  - Blast count > 100 x 109/L
  - Hepatosplenomegaly causing respiratory compromise
  - Heart failure
  - Renal or hepatic dysfunction
  - DIC with bleeding

Table 1. Selected TMD patient characteristics

	All TMD patients			TMD: observation only			TMD: intervention			
	n	%	Median (range)	n	%	Median (range)	n	%	Median (range)	Observation vs intervention, *P*
Total enrolled	139									
No. ineligible	4	3								
No. eligible	135	97		106	78.5		29	21.5		
Treatment arm at time of registration										
Observation	108	80.0		106	100		2	6.9		–
Received TMD intervention later	2	1.9								–
Leukopheresis/exchange transfusion	5	3.7					5	17.2		–
Chemotherapy (Ara-C)	22	16.3					22	75.9		–
Age at diagnosis, d			5 (0-58)			6 (0-52)			2 (0-58)	.061
Age at study entry, d			13 (1-66)			14 (2-66)			8 (1-61)	.004
Follow-up time, d			1153 (0-2857)			1151 (0-2857)			1196 (42-1923)	.978
Time to development of AML/MDS, d	21	16	441 (118-1085)	17	16	444 (118-1085)	4	14	280 (202-596)	.244

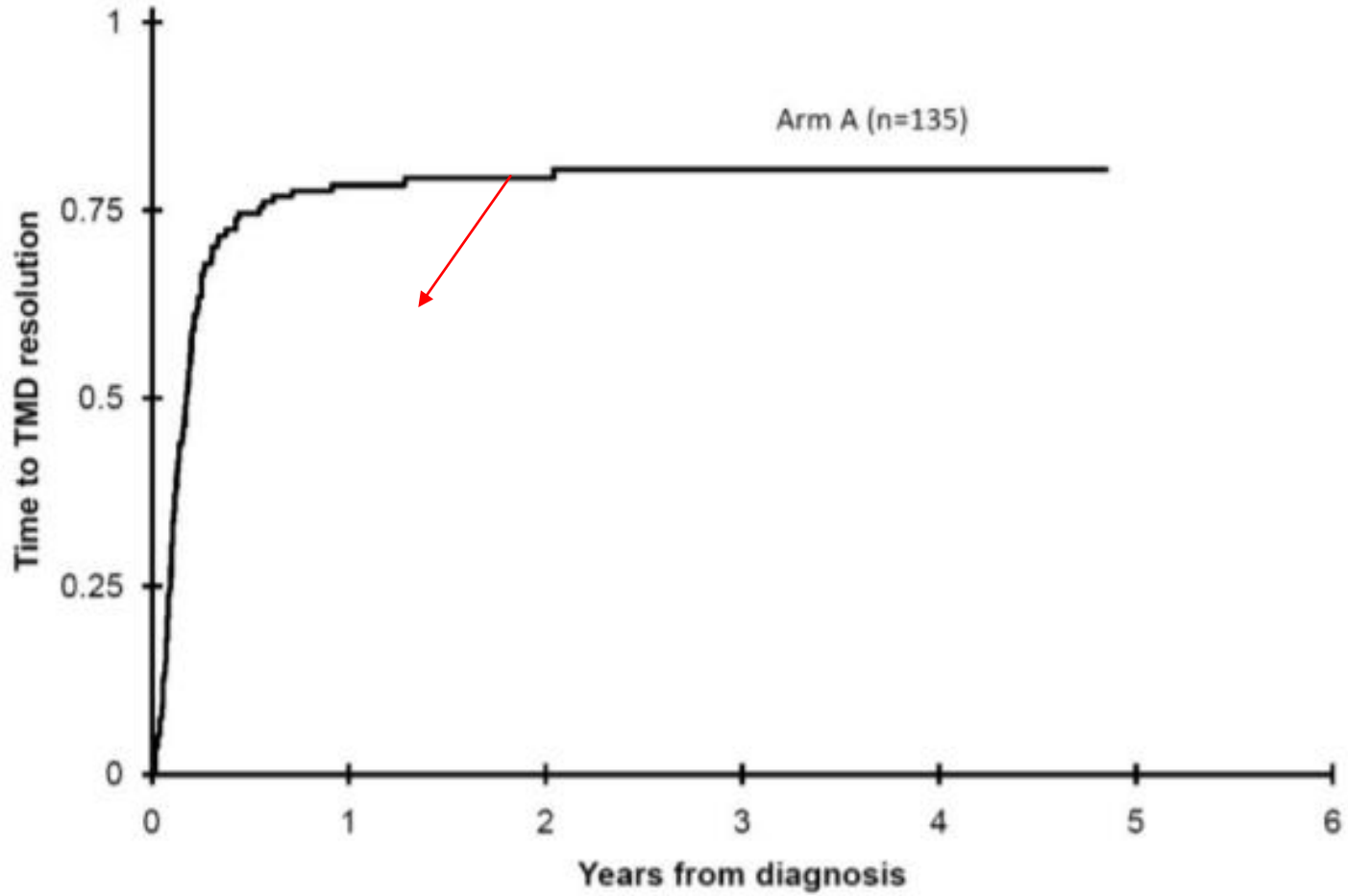

Figure 1. Time to TMD resolution from diagnosis for all patients enrolled.

Conclusion

- 10-20% children with DS have TMD, many mildly affected patients likely go undetected
- GATA-1 mutations are usually present
- Usually presents by 3 weeks of age
- Typically spontaneously regresses by 2-3 months
- Treatment is indicated when patients have life threatening symptoms


KEEP
CALM
ITS ONLY
AN
EXTRA
CHROMOSOME