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Transient Abnormal Myelopoiesis associated with down syndrome - etiopathogenesis, differential diagnosis and neonatal management: a literature review

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RESUMO

A Mielopoiese Anormal Transitória é uma desordem hematopoiética de natureza autolimitada, que acontece em fetos e neonatos portadores de Síndrome de Down que adquirem a mutação somática do GATA1. Apesar de sua característica benigna, parte dos pacientes podem apresentar formas graves da doença, com risco de desfecho fatal. Cerca de 20-30% destes, desenvolvem a Leucemia Mielóide Aguda secundária à Síndrome de Down, necessitando, impreterivelmente de quimioterapia. As vias etiopatogênicas e oncogênicas ainda não são bem definidas, assim como o manejo mais adequado. Este artigo se propõe a expor as principais publicações científicas da última década, buscando delinear fisiopatologia, diagnóstico e manejo. Para isso, foi realizada uma revisão sistematizada da literatura, buscando textos científicos originais, enquadrados no tema proposto, no que concerne ao diagnóstico diferencial, fisiopatologia, manejo e prognóstico do paciente no período neonatal. As informações combinadas dos textos incluídos nesta revisão, ratificam conceitos, delineiam classificações diagnósticas, descrevem manejos predominantes e propõem possíveis vias fisiopatológicas e estratificação prognóstica. No entanto, como foram poucos os estudos com alto poder de evidência identificados na última década, com predomínio de artigos observacionais não comparativos, não é possível ainda, baseado em evidências, propor um único modelo de etiopatogenia e uma clara estratificação prognóstica.

Palavras-chave: leucemia mielóide aguda. síndrome de down. doença mieloproliferativa transitória.

ABSTRACT

Transient Abnormal Myelopoiesis (TAM) is a self-limiting hematopoietic disorder which occurs in fetuses and neonates with Down Syndrome who acquire the GATA1 somatic mutation. Despite its benign characteristic, some patients may present severe forms of the disease, with the risk of a fatal outcome. About 20-30% of these develop acute myeloid leukemia secondary to Down Syndrome, which inevitably requires chemotherapy. The etiopathogenic and oncogenic pathways are not yet well defined, nor is the most appropriate management. This article aims to expose the main scientific publications of the last decade, seeking to delineate the pathophysiology, diagnosis and management of TAM. Thus, a systematic literature review was performed in searching for original scientific texts involving the proposed theme regarding the differential diagnosis, pathophysiology, management and prognosis of TAM patients in the neonatal period. The combined information from the texts included in this review ratifies concepts, outlines diagnostic classifications, describes predominant managements, and proposes possible pathophysiological pathways and a prognostic stratification. However, as there have been few studies with high a power of evidence identified in the last decade with a predominance of non-comparative observational articles, it is not yet possible to propose a single etiopathogenic model and a clear prognostic stratification based on evidence.

Keywords: acute myeloid leukemia. down syndrome. transient myloproliferative disorder.

INTRODUCTION

Transient Abnormal Myelopoiesis (TAM) is a myeloid haematopoietic disorder which despite becoming better known in recent years remains a challenge, especially about perinatal diag-

nosis, differential diagnosis, management and prognosis. According to the definition of the World Health Organization (2018), it consists of the only hematopoietic disorder which is present in Down Syndrome newborns, being cytomorphologically and clinically indistinguishable from acute myeloid leukemia [1]. It occurs almost exclusively in individuals with Down Syndrome (DS) and in the first month of life. However, there are reports of TAM in the literature in phenotypically normal children or in its mosaic form [2]. Even in these patients, chromosome 21 trisomy in clonal cells or the presence of the Gata1 gene mutation in exon 2 have been identified [3].

Down syndrome (DS) is a common inherited genetic disease characterized by chromosome 21 trisomy, affecting about 1.3% of pregnancies and about 1/100,000 live births [4]. These patients generally have high risk of hematological changes, even if benign, especially in the first weeks of life, as demonstrated in a prospective study of 135 DS children born between January 2009 to December 2015 in a hospital in Guadalajara-Mexico [5]. These children have a higher risk of about 150x for developing Acute Myeloid Leukemia of Down syndrome (AML-DS), and of about 40x for Acute Lymphoid Leukemia in children under 5 years of age [4, 6, 7]. Chromosome 21 alterations are certainly among the most important chromosomal and genetic alterations in the development of acute leukemia [4].

TAM occurs in about 10% of children with Down Syndrome, being self-limiting in about 60- 80% of cases and resolved without the need for chemotherapy [6, 8]. The real incidence of this disease in the world to date is unknown, but it is believed that these numbers are underestimated, requiring population and cohort studies. The disease may develop in the prenatal or neonatal period and presents various clinical and laboratory manifestations.

Intrauterine diagnosis is challenging, occurring in less than 5%, and in most cases confers a poor prognosis with a high rate of stillbirth and neonatal death in the first days of life [6]. Although clinical suspicion is easy to understand , its diagnosis can be complex, especially in the first weeks of life due to the similarity with Down Syndrome-associated Acute Myeloid Leukemia and the need for cytomorphological study of bone marrow and peripheral blood, cytogenetics, immunophenotyping and molecular biology techniques, which are often not accessible to many services.

In general, most TAM patients do not require chemotherapy; however, about 20% develop severe forms with leukocytosis, ascites, hepatic and cardiopulmonary involvement, disseminated intravascular coagulation and early death [6, 8]. In addition, about 20% of TAM patients develop Down Syndrome-associated Acute Myeloid Leukemia after the second year of life, demonstrating a probable correlation between these two conditions, and which is related to the presence of aneuploidy (trisomy of chromosome 21) and somatic mutation of GATA1 [8].

Most published scientific texts consist of case reports, case series and short narrative reviews, and systematic or integrative literature reviews dealing with this topic are still scarce. This article proposes to systematically review the literature, discussing etiopathogenesis, differential diagnoses, risk groupings and management of Transient Abnormal Down Myelopoiesis (TAM).

METHOD

The literature was systematically reviewed to perform this research using the PUBMED,

PERIODIC CAPES PORTAL, and BIREME/LILACS/MEDLINE databases. The Mesh Terms of the above research databases were defined and the following strategies were established: “Down Syndrome” AND “Transient Myloproliferative Disorder”; “Myeloproliferative Syndrome, Transient” AND “Down Syndrome” AND “Infant, Newborn”; “Myeloproliferative Syndrome, Transient” AND “Down Syndrome” AND “Infant, Newborn” AND “Leukemia, Myeloid, Acute”, with the non-standardized term “Transient Myloproliferative Disorder”. A search was also performed using the same strategies in the Cochrane Library but did not find any systematic reviews in the last 10 years addressing this theme in the neonatal period. The research was conducted in searching for articles from January 2009 to August 2019, in English, Spanish or Portuguese. The study design included cohorts with or without intervention, experimental studies involving human models, as well as comparative and non-comparative observational studies. Experimental studies with exclusively animal models, non-original studies (reviews) or editorials were excluded. A correlated systematic review was identified using the PUBMED database; however, even though it was correlated, it did not address the proposed objectives of this review, as it exclusively addressed prenatal diagnosis and management.

After applying the searching strategies described above, the scientific texts were selected in an initial screening based on title and abstract. Then the selected articles were submitted to a methodological evaluation of the evidence quality and data extraction by two independent reviewers. In the event of disagreement among the reviewers, a scientific debate was held to reach consensus. Agreement was quantified by the Kappa statistical method.

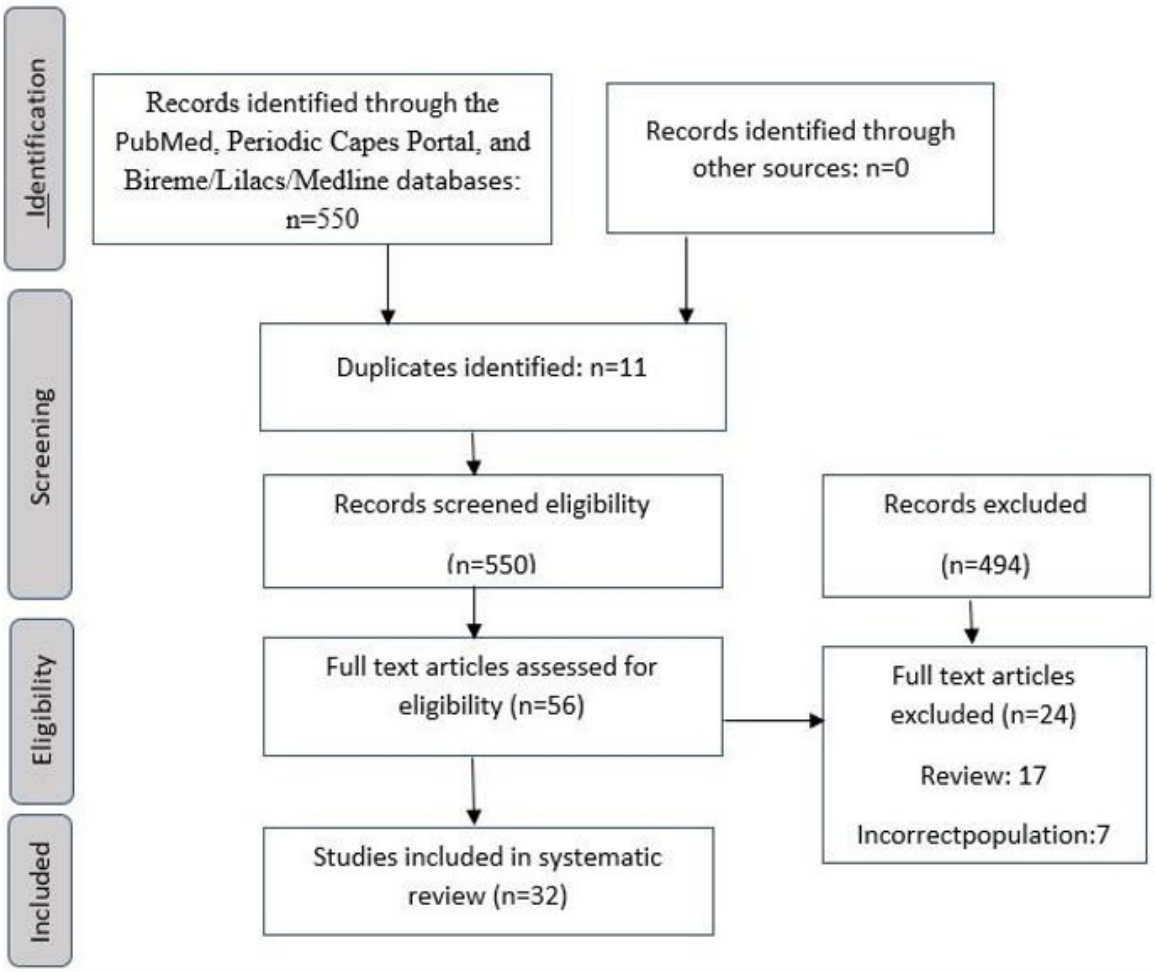
RESULTS

A total of 550 related articles were found through the strategy described above. We then obtained a final number of 32 articles in the outlined period by applying the filters and removing the duplicates, review studies, editorials, non-human experiments. Results were compiled following the format "Preferred Report Items for Systematic Reviews and MetaAnalyzes" (PRISMA)[9] (Fig. 1). According to the inclusion criteria, the studies were evaluated by two independent reviewers, with the degree of agreement quantified through the Kappa statistical test. The agrement on the inclusion between the two revierwers was 87%, with k: 0,724, considered substantial.[10] Two articles disagreed with the reviewers’ analysis and were included after scientific discussion. Among the included articles, there are 02 prospective cohorts with intervention; 08 observational studies (cross-sectional and retrospective); 02 experimental studies; and 19 case report studies and case series. The evidence quality of the scientific texts was evaluated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE), with 61,3% having a “very low” rating; 6.45% having “high”, and the others “moderate” to “low”, demonstrating the scarcity of well-delineated clinical trials and observational studies with adequate sampling and more consistent results. This fact (among other factors) is related to the rarity of the disease and the diagnostic limitations.

Two studies proposed to define risk populations, prognostic factors, evolution, efficacy and therapeutic toxicity [11, 12]; 10 studies addressed leukemogenesis, etiopathogenesis, and biomarker models [13-20]; 02 studies proposed experiments involving human models to study etiopathogenesis and epigenetic pathway [21, 22].

When evaluating only the non-comparative observational studies researched and compiled in this article, there are 26 cases of TAM and 04 cases of AML-DS [23-39]. Of these, 23% received cytarabine chemotherapy, with low doses (1.5mg/kg, IV or SC, 7 days) being the predominant dosage [23, 25, 27, 29, 31, 36]. The main causes of initiating treatment were hyperleukocytosis and acute liver dysfunction (with or without fibrosis), followed by respiratory failure and "Cutaneous leukemia" associated with leukocytosis and visceromegaly. Two cases died due to TAM-related complications and 05 developed AML-DS [24, 28, 32, 33, 39].

Figure 1 - Flow chart record selection for imclusion im the literature review



DISCUSSION

Transient Abnormal Myelopoiesis (TAM), also called Transient Leukemia or Transient Myeloproliferative Disorder, is a condition recognized by the World Health Organization's Classification of Hematopoietic Tumors and Lymphoid Tissues. By definition, it is associated with Down Syndrome or its mosaic form, and is clinically and laboratory indistinguishable from Acute Myeloid Leukemia of Down syndrome (AML-DS) [1, 26]. In addition, there are cases of this pathology in patients who do not have this chromosopathy phenotype, but with chromosomal alteration in the clonal cell [30, 33].

The literature has reported cases of Transient Myeloproliferative Disorders outside the context of Down Syndrome and the somatic mutation of the GATA1 gene [40], however, considering the World Health Organization Classification of Hematopoietic Tumors and Lymphoid Tissues, this condition cannot be called TAM associated with Down Syndrome, and is therefore

not yet defined and controversial. Down syndrome (DS) is known to be one of the aneuploidies which most increases the risk of secondary acute leukemia, with the risk of acute lymphoid leukemia (ALL) being around 10-20x, and acute megakaryocytoblastic leukemia 500x [18]. Despite the similarity between TAM and AML-DS, the literature does not conceptually impose the need for > 20% bone marrow blast infiltration and/or peripheral blood to characterize this transient disorder, nor does it determine the amount of blasts required for diagnosis, not clarifying the defining criteria of the disease in clinical practice [1]. Therefore, in order to try to standardize the diagnosis and management of these patients, the British Society of Hematology published a guideline in 2018, which recommends that the TAM diagnosis in neonates be made by identifying the somatic mutation of GATA1 associated with the presence of peripheral blood myeloblasts > 10% or more in children with Down syndrome or its mosaic form, with clinical laboratory findings suggestive of TAM [41].

Despite the easy clinical suspicion, what is observed in practice is a difficulty of diagnostic confirmation, especially considering the need to assess the mutational status of GATA1. In addition, blasts infiltrating into the peripheral blood is often more exuberant than in the bone marrow [29], possibly being related to some degree of spinal cord fibrosis [14, 26], which could lead to various diagnostic difficulties if it is mandatory to identify the classic criteria for diagnosing acute leukemia (≥20% of peripheral blood and/or bone marrow blasts, according to the World Health Organization). About 5-10% of children with Down Syndrome develop prenatal disease, making their diagnosis even more challenging and one of the most important causes of non-immune fetal hydrops in this setting [12, 25].

Soler *et al.* (2011) identified the following immunophenotypes of the studied AML-DS and TAM patients: expression of CD34, CD45, CD117, CD7, variable CD13, CD33, CD64, CD11b, CD5, CD56, HLA-DR, CD61, CD41, and CD42, characterizing a predominantly megakaryocytic and sometimes erythroid myeloid phenotype, with anomalous expression of CD56 and CD7. In fact, these profiles have been repeatedly found by several authors in patients with TAM and later in AML-DS, both of which are virtually indistinguishable in terms of cytological and immunophenotypic characteristics [24, 26, 27, 29]. Thus, from the epigenetic point of view, TAM and AML-DS are correlated and also show many similarities [21].

Most TAM patients have no life-threatening signs or symptoms, and progress favorably with disease remission within the first three months of life without any intervention [12]; however, some neonates develop severe forms of the disease, requiring treatment and often progressing to a fatal outcome [11]. Among the most frequent manifestations of TAM is leukocytosis, which may be hyperleukocytosis (>100,000 cel/mm3); anemia or polyglobulia; the presence of peripheral blood blasts; thrombocytopenia; lymphadenopathy; or hepatosplenomegaly. Although the patient commonly presents with thrombocytopenia of varying degrees, there are reports of thrombocytosis, sometimes exceeding 1,000,000 cells/mm3 [29]. Some neonates have vesicopustular cutaneous lesions located on the face, trunk and extremities associated with the underlying disease called “cutaneous leukemia” [28, 36-38]; 10 to 20% have complications such as liver failure with or without fibrosis, hepatosplenomegaly with respiratory failure, serositis, cardiovascular damage, disseminated intravascular coagulation (DIC), and may progress to death [17]; while 20 to 30% of these patients develop AML-DS after the fourth to seventh month of life and up to the fourth year, and in this case need chemotherapy treatment [14].

Furthermore, as a small percentage of TAM which evolves into severe, life-threatening forms, there is no clear definition of the reasons for this malignant evolution, and unambiguous prognostic factors are unknown. However, in an important study by Maeda *et al.* (2016), the authors suggest that high IL8 expression in patients with unfavorable clinical course (especially acute liver fibrosis) is a marker of severity and prognosis. Certainly, IL8, which is one of the most important innate immunity-enhancing chemokines, promotes an increased release of reactive oxygen species (ROS) by neutrophils in migration tissue, enhancing inflammatory lesion and possible local fibrosis. However, this inflammatory pathway is not fully understood, let alone the role of IL8 as a severity marker. Other authors have already shown an increase in IL8 and other cytokines such as IL7 and TGFβ1 in this scenario, corroborating the inflammatory pathway as an important target organ fibrosis model, with the liver being the most affected [39]. On the other hand, in vitro experiments have shown the presence of monocyte chemoattractant protein 1 (MCP1) in the serum and urine of neonates with hepatic fibrosis and TAM, suggesting that this is an important fibrosis marker via activation of hepatic stellate cells [22].

There is also pericardial effusion among the clinical manifestations of TAM, which can lead to cardiovascular collapse. Non-comparative observational studies have identified an increase in Hepatocyte Growth Factor (HGF) in the serum and organic fluid of these patients [35]. It is a protein derived from mesenchymal cells which acts on endothelium formation, scarring and organogenesis, and may be involved in the development and severity of serositis, especially pericardial effusion [35].

The etiopathogenesis of TAM is not yet well understood, however it is observed that the presence of chromosome 21 trisomy associated with the somatic mutation of the GATA1 gene plays a key role in this outcome [14-17]. For Nikolaev *et al.* (2013), the presence of the GATA1 mutation is not found without chromosome 21 trisomy. On the other hand, according to the same authors, this aneuploidy is capable of conferring hyperproliferative potential in the bone marrow, especially in the malariocytic lineage. Perhaps this partly explains the frequent haematological alterations of this syndrome, despite the presence of TAM.

Regarding GATA1, it is a gene located on the Xp11.23 chromosome, which produces a “zinc-finger” transcription factor, being essential for the normal development and terminal maturation of erythrocytes and especially megakaryocytes [13, 14, 17, 26, 28]. These mutations mostly occur in exon 2 and are deletion, insertion and point mutations, with the latter being more frequent [15, 18]. The GATA1 mutation encodes a shorter protein resulting from of an early stop codon (GATA1s), with loss of the dominant N-terminal region, compromising the normal development of erythrocytes and especially megakaryocytes. Although GATA1 mutation associated with chromosome 21 trisomy is the basis of TAM etiopathogenesis, other genes certainly collaborate in this process. Takahashi *et al.* (2015), identified the DYRK1A, ERG and ETS genes in the 10.7Mb enlarged region of 21q22.12– 21q22.3 in a TAM case, which is believed to correlate with the origin of this condition. Added to this is the fact that there are often changes in folate metabolism with folate entrapment in its 5-methytetrahydrofolate (5 me-THF) form in DS, causing inhibition of the thymidylate synthase enzyme and incorporation of uracil into the DNA strand [16, 42]. All of these events may be potentiated by the overexpression of cystathionine beta synthase (CBS), which accelerates folate metabolism and reduces DNA repair capacity, contributing to the etiopathogenesis of TAM and AML-DS [16].

AML-DS patients also present chromosome 21 trisomy and GATA1 mutation as the core of leukemogenesis, which denotes a convergence between these two pathologies (TAM and AML-DS), and therefore a likely clonal correlation [14]. However, there is a need for other events such as other somatic genetic changes for the patient to develop AML-DS [28]. It is not clear whether there is any GATA1 mutation profile that may predispose these individuals to develop AML-DS years later. In a retrospective observational study, Alford *et al.* (2011) evaluated GATA1 mutation mapping in 134 patients with TAM and 103 with AML-DS from blood or bone marrow samples at two reference centers (UK and Germany), and identified no differences between mutation types for these two pathologies. Nikolaev *et al.* (2013) performed the genetic mapping of 10 newborns with TAM, 07 with AML-DS, and 02 AML-DS in remission. They identified few mutations and an absence of chromosomal instability in the TAM group, different from AML-DS. For these same authors, multiple mutations in EZH2, APC and JAK/STAT, MAPK/PI3K, and WNT seem to contribute to the evolution of TAM in AML-DS [13], generating different epigenetic silencing, tumor suppression, cell maturation and proliferation processes.

Recently, an important experiment traced the DNA methylation profile of AML-DS patients in order to enable better understanding of the process epigenetics, showing a series of gains and losses of “methyl radical” occurring at specific moments of cellular metabolism [21].

The true incidence of TAM among patients with Down syndrome is not known, nor is it possible to confirm the disease by clinical-hematologic manifestations alone. In addition, we seek to elucidate the actual risk defining prognostic factors for TAM and AML-DS. Based on these questions, Roberts *et al.* (2013) published an interesting observational, prospective, multicenter, non-randomized study involving 18 UK hospitals, where 200 DS neonates were recruited from October 2006 to March 2012, with the primary objective to identify at risk populations for TAM. More than 95% of the study population had peripheral blood blasts; however, only 17.5% of neonates had TAM criteria (defined as > 10% peripheral blood blasts and presence of GATA1 mutation), 8.5% with clinical-hematological manifestations (classic TAM). Eighteen [18] neonates had few peripheral blood blasts (median 5%) with no clinical symptoms, and GATA mutation only identified by Next-generation sequencing (NGS), referred to as “silent TAM”. Despite the high percentage of individuals with peripheral blood blasts (confirming frequent hematological changes in DS), only GATA1 mutated neonates evolved to AML-DS. Four children evolved to AML-DS (11.4% of patients with TAM), 3 from neonates who presented classic TAM and 01 from “silent TAM”. Therefore, the authors of this study confirm the importance of GATA1 mutational status in TAM and AML-DS etiopathogenesis, and suggest that TAM diagnosis is not solely based on aneuploidy (Trisomy 21) associated with clinical-hematological findings, but also in the presence of the GATA1 mutation, identified by Direct High-Pressure Liquid Chromatography (DHPLC) or NGS (17). Queiroz *et al.* (2013) failed to identify this mutation in 2 newborns with DS who developed TAM when performed by direct sequencing by PCR, denoting the need to improve the technique, as already pointed out by the study described above [17].

There are certainly other unclear leukemogenic pathways for patients who develop TAM associated with non-germinal chromosopathy and somatic GATA1 mutation. Haemmerling *et al.* (2012) described a TAM case in a CHARGE syndrome neonate (coloboma, heart disease, nasal choanal atresia, growth and developmental delay, genital hypoplasia, pinna abnormalities/deafness). The same case presented chromosome 21 trisomy in the clonal cell, evidence of GATA1 mutation and 15q24 microdeletion. It is known that this microdeletion leads to impairment of the

PML tumor suppressor gene, promoting suppression of the GATA1 and GATA2 genes, and thus contributing to the megakaryocytic differentiation deficit [34]. Although not yet a fully proven hypothesis, this seems to be a possible oncogenesis pathway in the non-germinative chromosome 21 trisomy scenario.

Despite all that is known about this topic, deciding who should be treated or whether the established therapy will impact a future disease can be difficult. The Children's Oncology Group study A2971 evaluated 135 newborns with DS and TAM for 5 years. Of these, 28% had life-threatening signs and symptoms (hyperviscosity, blasts > 100,000cells/mm3, hepatosplenomegaly, respiratory failure, heart failure not directly related to DS, fetal hydrops, hepatic and renal insufficiency, disseminated intravascular coagulation - DIC) and were treated with an exchange-transfusion and/or cytarabine (3.33mg/kg/24h IV) for 5 days, administered every 14 days for up to three cycles with high myelotoxicity (96% grades 3,4). As a result 16% developed AML-DS during the follow-up period, with no difference between the groups treated and not treated for TAM. The major risk factor for AML-DS was the resolution time of TAM (greater than or less than 47 days), with 21% overall mortality and 10% being TAM-related [11]. Later, a multicenter, non-randomized, historical-controlled German study (TMD07) recruited 105 patients with DS, with > 5% peripheral blast and/or medulla blasts of bone and presence of GATA1 mutation in exons 1, 2 or 3 to assess whether low-dose cytarabine treatment would reduce the progression rate of these patients to AML-DS. In this study, the cumulative AML-DS incidence in treated patients was 25%, similar to historical control (22%); however, the cumulative incidence of early death was lower compared to historical control, suggesting that early treatment with low cytarabine doses in symptomatic patients reduces TAM mortality [12]. Unlike study A2971, the German study showed good tolerance and low toxicity to the proposed chemotherapy treatment [12] (Table 1).

Table1. Information Between Two Transient Abnormal Myelopoiesis Cohorts

Study	Death	Year	(N)	Fallow-Up (median)	EFS*	OS**	Treatment
GAMIS, et al 2011	21% (all patients study) 10% (TMD)	1999-2004	135	1153 days	57% (all patients: 3year%) Intervention patients: 33% (3 year%)	-77% (all patients; 3- year%) -Intervention patients: 51% (3-year%)	Cytarabine-3,33mg/kg/24 h IV, 5 days (3 courses)
FLASIN SK, et al 2018	9% (AML+TMD) 4,9% (TMD)	2007-2015	102	1083 days	72% (em 5 anos)	91% (all patients; 5 year%)	Cytarabine 1,5mg/kg SC ou IV, 7 days (3 courses)

***EFS- Event-Free Survival; **OS: Overall Survival; TMD: Transient Myeloproliferative Disorder; AML: Acute Myeloid Leukemia**

From all that has been discussed and presented, it is possible to state that as a rule, these patients have good sensitivity to low dose cytarabine-based chemotherapy, which is linked to metabolic changes related to chromosome 21 [28]. For Reyes *et al.* (2014), the chemosensitivity of TAM and AML-DS is related to overexpression of cystathionine beta synthase observed in DS or its mosaic form, leading to serum increase of Ara-CTP, the active intracellular metabolite of cytarabine, contributing to increased toxicity. In addition, GATA1s mutated truncated protein interferes with the expression of cytidine deaminase (CDA), which is responsible for the hydrolytic deamination of cytarabine in its inactive uracil form [28].

Therefore, low-dose cytarabine is so far recognized as the "gold standard" chemothera-

peutic treatment in this setting, and is even recommended by the British Hematology Society as a guideline [41]. Li et al (2018) evaluated 25 cases of hematopoietic disorders associated with Down Syndrome, 35% with TAM, 24% with Megacarioblastic Acute Myeloid Leukemia, 4% Acute Lymphoblastic Leukemia and the others, other acute myeloid leukemia. The overall survival rate was 40%, considered low. However, it is necessary to consider that patients with acute leukemia, not only with TAM, and undergoing different chemotherapy protocols were included in this sample [43].

Although some questions are not yet fully understood and etiopathogenic models are not properly delineated and proven, the advances in understanding the biological behavior and management of this myeloproliferative disease is undeniable. In light of the scientific literature, this review presented definitions, described leukemogenesis pathways and attempted to identify risk groups for TAM and AML-DS; however, > 50% of the studies listed in this review have a “very low” quality of evidence (GRADE classification), and so it is not possible to propose a single etiopathogenic and management model based on evidence. It is a fact that this topic is still far from being exhausted, and new well-designed studies with the broad cooperation of the various reference centers in the world are needed to deepen their understanding, thereby bringing benefits to clinical practice.

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