Chapter 7

Sociodemographic and Birth Characteristics in Infant Acute Leukemia: A Review

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1. Introduction

Acute leukemias are cancers of the hematopoietic system that involve, in the majority of cases, a malignant transformation of myeloid and lymphoid progenitor cells [1]. Acute leukemias represent the most common type of childhood cancer [2,3]. Acute lymphoblastic leukemia (ALL) has a frequency of five times greater than that of acute myeloblastic leukemia (AML) and is the most common cancer in children, representing 25% to 35% of all childhood cancers [3,4]. The incidence of ALL varies significantly among developed and developing countries. With a reported annual incidence of 20-45 cases per million children, the highest incidence rates are recorded in the Hispanic population in California, Texas and Florida and in Costa Rica and the City of Mexico [4-7]. Despite advances in therapy and improvements in survival, acute leukemia represents one of the main causes of morbidity and mortality in children. The etiology of this disease remains unknown. Only Down syndrome and ionizing radiation have been recognized as risk factors for the development of childhood acute leukemia [8]. However, the risk attributable to these factors is very small. Epidemiological studies exploring different environmental exposures along with advances in cytogenetics and immunophenotyping have identified different subgroups of the disease that must be considered separately. Such is the case of infantile leukemia. Although it is a rare disease in this group, the molecular characteristics and survival are different in infants than in older children, suggesting that the etiology is distinct and most likely involves prenatal factors. The purpose of this chapter is to introduce the reader to a systematic review of the current literature on reported risk factors for childhood acute leukemia (AL). This review reports what is currently known about acute leukemia in infants and future directions.

2. Descriptive epidemiology

Leukemia in infants (<1 year) is an extremely rare disease, and few studies exist that explore the incidence of leukemia in this age group. Parkin et al., reporting incidence rates for this age group in different regions of the world, determined that Mexico recorded the highest incidence rate in children <1 year for the study period, exceeding the rates of the United States, some countries in Latin America, Europe, Asia and Oceania [5]. However, United States, Great Britain, and Australia have some of the highest incidence rates for infantile ALL, with approximately 20-40 cases per million children, whereas countries like Brazil and Cuba have reported rates of approximately 8-12 cases per million children. The Hispanic population of infants in Los Angeles, Japan and Australia has been reported to have the highest AML incidence rates of approximately 10-12 cases per million children. As with ALL, Brazil and Cuba have some of the lowest incidence rates, with approximately 3-5 cases per million children [6].

Descriptive epidemiological studies conducted in Mexico City on acute leukemia and childhood cancer have consistently identified a significant incidence for AL in the infant population. In the 1980-1992 study period, in newborns population ALL occupied the third place as the main type of cancer and the second place in the infant population and after 2 years of age, a very important peak in AL development is observed [9]. For the period 1996-2002, the incidence of AL in infants was 37.5 per 10^6 children [10,11], and between 1996 and 2006 another study reported an incidence of 33.0 ALL cases per 10^6 children < 1 year of age [12]. The most recent survey of childhood AL in 2006-2007 in Mexico City reported an incidence rate of ALL and AML of 24.3 and 4.1 per 10^6 infants, respectively [7].

Epidemiological studies in infants are rare. However, there is a predominance of females in infants with ALL, whereas in children older than 1 year, male are more frequently diagnosed [13]. Because of the young age of presentation of infantile leukemia, studies are focused specifically on pre-conception exposures during pregnancy as potentially relevant exposures that occur *in utero* or shortly before pregnancy. That is, the window of study for the disease in this cohort is very short – approximately 9 months. Therefore, the study of this group can provide essential information not only for this group but also for the development of childhood AL [14,15]. The epidemiological studies have evaluated maternal exposure during pregnancy to different risk factors that could be associated with the development of leukemia in infants. These studies are presented in table 1 and include the publication of epidemiological studies in the last 12 years in the infant population and its association with AL. Although the studies are interesting and provide important information, some studies have failed to find significant associations because they have some methodological limitations, such as sample size (small number of exposed individuals among subgroups) or incomplete and biased exposure assessment (not validated). In some cases they have a low response rates between cases and controls. It is important to consider these aspects for future association studies. Despite these limitations, these studies provide an important contribution to the limited amount of existing studies linking infants with AL and risk factors.

Variables studied	Study design	Cases analyzed	OR (95% CI)	Conclusions	Author and year
Maternal exposure to household chemicals	Case-control	264 ALL 172 AML 7 Other	Petroleum products Any ALL OR 1.56 (0.90-2.70); AML OR 2.33 (1.30-4.18); MLL+ OR 1.38 (0.77-2.48) Month before pregnancy ALL OR 1.31 (0.71-2.41); AML OR 1.42 (0.71-2.83); MLL+ OR 1.14 (0.58-2.21) During pregnancy ALL OR 1.60 (0.90-2.83); AML OR 2.54 (1.40-4.62); MLL- 2.69 (1.47-4.93)	Gestational exposure to petroleum products was associated with infant leukemia, particularly AML and MLL-.	Slater et al., 2011[23]
Analgesic use during pregnancy	Case-control	262 ALL 172 AML	Before knowledge pregnancy Any use Aspirin ALL OR 1.03 (0.58-1.85) AML OR 0.55 (0.24-1.26) Non-aspirin non-steroidal anti-inflammatory drugs (NSAID) ALL OR 1.15 (0.80-1.67) AML OR 0.60 (0.37-0.97) Acetaminophen ALL OR 1.16 (0.80-1.68) AML OR 0.66 (0.43-1.01) After knowledge pregnancy Any use Aspirin ALL OR 1.21 (0.48-3.05) AML OR 0.96 (0.32-2.92) NSAID ALL OR 1.33 (0.75-2.37) AML OR 0.81 (0.36-1.83) Acetaminophen ALL OR 1.03 (0.70-1.53) AML OR 0.79 (0.50-1.24)	Analgesic use during pregnancy was not significantly associated with the risk of infant leukemia.	Ognjanovic et al., 2011[24]
Maternal prenatal cigarette, alcohol and illicit drug use	Case-control	264 ALL 172 AML 7 Other	During pregnancy Cigarette use OR 0.80 (0.52-1.24) ALL OR 0.87 (0.54-1.40)	Cigarette smoking was not associated with childhood leukemia; alcohol and illicit drug use were not consistent with prior reports.	Slater et al., 2011[25]

Variables studied	Study design	Cases analyzed	OR (95% CI)	Conclusions	Author and year
			AML OR 0.74 (0.40-1.35) Alcohol use OR 0.64 (0.43-0.94) ALL OR 0.64 (0.43-0.94) Illicit drug use OR 0.69 (0.40-1.18) ALL OR 0.84 (0.47-1.51) AML OR 0.52 (0.23-1.16)		
Maternal vitamin and iron supplementation	Case-control	264 ALL 172 AML	Prenatal Vitamins OR 0.79 (0.44-1.42) ALL OR 0.63 (0.34-1.18) AML OR 1.20 (0.53-2.75) Iron supplements OR 1.07 (0.75-1.52) ALL OR 1.22 (0.82-1.80) AML OR 0.82 (0.51-1.33) Periconceptional Vitamins OR 0.89 (0.64-1.24) ALL OR 0.77 (0.54-1.11) AML OR 1.05 (0.68-1.61) Iron supplements OR 1.23 (0.63-2.38) ALL OR 1.30 (0.62-2.72) AML OR 0.77 (0.46-1.27) During pregnancy Vitamins OR 0.78 (0.48-1.28) ALL OR 0.66 (0.39-1.11) AML OR 1.05 (0.55-2.04) Iron supplements OR 1.06 (0.74-1.53)	The authors did not observe a prenatal vitamin-infant leukemia association.	Linabery et al., 2010 [26]

Continued…

Variables studied	Study design	Cases analyzed	OR (95% CI)	Conclusions	Author and year
			ALL OR 1.22 (0.81-1.84) AML OR 0.77 (0.46-1.27)		
Congenital abnormalities	Case-control	264 ALL 172 AML 7 Other	Congenital abnormality (CA) OR 1.2 (0.8-1.9) Birthmarks OR 1.3 (0.7-2.4) Urogenital abnormalities OR 0.7 (0.2-2.0) Other CA OR 1.4 (0.7-2.8)	The authors did not find evidence for a link between CAs and infant leukemia	Johnson et al., 2010 [27]
Parental infertility and infertility treatment	Case-control	264ALL 172 AML	Women not trying to conceive OR 1.62 (1.01-2.59) ALL OR 2.50 (1.36-4.61) AML OR 1.17 (0.61-2.22) Women with ≥1 year of trying OR 0.99 (0.47-2.07) ALL OR 2.01 (0.85-4.78) AML 0.35 (0.09-1.27)	There were no positive associations between parental infertility or infertility treatment and infant leukemia.	Puumala et al., 2010 [28]
Dipyrone	Case-control	132 Acute leukemia	N-Acetyltransferase 2 (NAT2) dipyrone during pregnancy OR 5.19 (1.86-14.5)	NAT2 slow-acetylation profiles associated with infant leukemia &dipyrone	Zanrosso et al., 2010 [29]
Birth weight	Case-control	148 ALL 53 AML	Birth weight >3999 g OR 1.59 (0.79-3.17) ALL OR 2.28 (1.08-4.75) MLL+ OR 2.68 (0.99-7.15)	The results suggest that high birth weight is associated with an increased risk of infant leukemia.	Koifman et al., 2008 [30]
Birth characteristics and maternal reproductive history	Case-control	149 ALL 91 AML	Birth weight ≥4,000 g OR 1.09 (0.67-1.79) Gestational age <37 weeks OR 0.74 (0.32-1.70) Birth order 2nd OR 0.60 (0.40-0.91) Maternal age ≥35 years OR 0.75 (0.46-1.23)	Maternal history of fetal loss and other birth characteristics were not related to infant leukemia.	Spector et al., 2007 [31]

Variables studied	Study design	Cases analyzed	OR (95% CI)	Conclusions	Author and year
			Prior fetal loss Any OR 1.04 (0.70-1.55) Pre-pregnancy BMI 25-29.9 OR 1.61 (1.04-2.48) Weight gain during pregnancy (kg)>18.14 OR 1.50 (0.84-2.68)		
Maternal anemia	Case-control	178 Acute leukemia	Anemia during pregnancy (<11 g dl^{-1}) OR 0.93 (0.57-1.53) ALL OR 1.14 (0.65-2.01) AML OR 0.67 (0.32-1.37) ALL/MLL+ OR 0.98 (0.50-1.91) AML/MLL- OR 0.57 (0.16-2.07)	The authors did not find evidence for an increased risk of leukemia in the offspring of mothers with hemoglobin <11 g dl^{-1} during pregnancy.	Peters et al., 2006 [32]
Maternal illicit drugs, pain medication, vitamins/iron supplement, folic acid, hormones, abortive drugs, herbal infusions, pesticides during pregnancy	Case-control	202 Acute leukemia	TobaccoORa 0.89 (0.63-1.25) MarijuanaORa 0.87 (0.63-1.20) DipyroneORa 1.45 (1.02-2.06) Amoxicillin ORa 0.88 (0.63-1.25) Folic acid ORa 1.22 (0.73-2.05) MetronidazoleORa 1.39 (0.82-2.34), MisoprostolORa 1.23 (0.38-4.02) Hormones ORa 8.76 (2.85-26.93) Herbal infusions ORa 1.93 (0.49-7.58) Pesticides ORa 2.18 (1.53-2.13) Hormones intake: Preconception OR 2.26 (1.21-4.21); MLL+ OR 3.34 (1.51-7.36) 1st trimester OR 11.35 (3.20-40.20); MLL+ OR 10.57 (2.33-47.91) 2^{nd} trimester OR 4.49 (1.07-18.87); MLL + OR 2.62 (0.15-17.56) 3^{rd} trimester OR 2.32 (0.60-8.98); MLL+ 1.02 (0.10-9.93)	A statistically significant association between the maternal use of hormones during pregnancy and infant leukemia.	Pombo-de Oliveira et al., 2006 [33]
Maternal diet (DNA topoisomerase II	Case-control	149 ALL 91 AML	DNAt2 inhibitor with MLL+ Quartile 4 OR 0.7 (0.4-1.5)	Maternal consumption of vegetables and fruits were associated	Spector et al., 2005 [34]

Variables studied	Study design	Cases analyzed	OR (95% CI)	Conclusions	Author and year
inhibitor)			ALL OR 0.5 (0.2-1.1) AML OR 3.2 (0.9-11.9) Vegetable and fruits plus index Quartile 4 OR 0.6 (0.3-1.1) ALL OR 0.5 (0.2-0.9) AML OR 1.1 (0.4-2.9)	with a decreased risk of infant leukemia, particularly MLL+. DNAt2 inhibitors increase the risk of AML (MLL+).	
Maternal smoking, alcohol, DNA damaging drugs, herbal medicines, pesticides, Dipyrone, insecticides	Case-control	49 ALL (19 MLL+) 74 AML (29 MLL+) 13 Other (2 MLL+)	Smoking ALL OR 1.59 (0.82-3.07); AML OR 1.33 (0.63-2.80); MLL+ OR 0.98 (0.46-2.09) Alcohol ALL OR 0.63 (0.25-1.60); AML OR 1.92 (0.90-4.10); MLL+ OR 0.74 (0.29-1.90) DNA Damaging drugs ALL OR 1.78 (0.95-3.34); AML OR 2.28 (1.10-4.71); MLL+ OR 2.31 (1.06-5.06) Herbal medicines ALL OR 4.45 (2.06-9.63); AML OR 2.09 (0.89-4.92); MLL+ OR 3.00 (1.38-6.54) Maternal Pesticide ALL OR 2.53 (0.71-8.97); AML OR 5.08(1.84-14.04); MLL+ OR 4.96 (1.71-14.43) Dipyrone ALL OR 3.13 (1.02-9.57); AML OR 3.01 (0.93-9.79); MLL+ OR 5.84 (2.09-16.30) Insecticides ALL OR 4.30 (0.66-28.08); AML OR 7.82 (1.73-35.39); MLL+ OR 9.68 (2.11-44.40)	The data suggest that specific chemical exposures of the fetus during pregnancy may cause MLL gene fusions.	Alexander et al., 2001 [35]

Table 1. Risk factors for infant leukemia studied in the last 12 years.

3. Clinical characteristics

Infants with leukemia possess different molecular genetics features, immunophenotypes and cytogenetic characteristics with respect to older children. Infants with ALL have a very high leukocyte count (hyperleukocytosis); the median of leukocyte count in infants with ALL was

recorded as 100 x 10^9 L. Infants with ALL also often exhibit hepatosplenomegaly, widened mediastinum, and compromise of the central nervous system (CNS) in approximately 15% of cases. In addition, 13% of male infants exhibit infiltrated testes [16,17]. The ratio ALL/AML in infants is approximately 1.5-2.0, and the M4 or M5 morphology predominates in infants diagnosed with AML [5,18,19].

A significant proportion of infants diagnosed with ALL are characterized by a very immature precursor B-lineage ALL – pro B CD-10. The mature B-lineage ALL is very rare and only 4% of cases are of T-lineage [13]. The leukemic cells of infants with ALL express myeloid antigens, which may indicate that this type of leukemia is generated in immature precursor cells that have no lymphoid differentiation [17]. Unlike older children diagnosed with ALL, with a 5-year survival rate of 80%, infants with leukemia have a very poor 5-year survival rate of 50% or less. The 5-year survival rate for infants with AML is 40%, similar to that reported in older children [20-22].

4. Genetic characteristics in infants

Both ALL and AML in infants are frequently associated with abnormalities (genetic rearrangements) involving the Mixed Lineage Leukemia (MLL) gene, also called Htrx, ALL-1 or HRX, which is located on chromosome 11 band q23 [36-38]. This gene is fused promiscuously with different pairs of chromosomes; up to 70 partners have been reported in human leukemia [39]. The most common fusion partners include chromosome 4, reported in 50% of cases; chromosome 11, with a frequency of 20%; and chromosome 9, present in 10% of cases. Fusions of chromosome 9 are presented in older infants, unlike fusions of chromosomes 4 or 11 [40,41]. The ENL chromosome has also been found fused with MLL, although at a lower frequency [38]. Infants with the MLL gene have a very poor prognosis compared with older children with the disease [13,42,43].

MLL translocations are present in 75-85% of ALL infants less than 1 year and in 60% of infant AML casesMLL translocations are found in older children and are reported in 5% of cases of childhood AL and 85% of leukemias secondary to treatment with topoisomerase II inhibitors, which are usually AMLs [37,42,44,45]. This last frequency is very important because it has implications for the etiology of leukemia in infants.

5. Structure of the MLL gene

The MLL gene is located on chromosome 11q23 just after the repressor domain. The MLL gene is 90 kb, consists of 38 exons, and produces a 12-kb mRNA that encodes a 430-kDa protein of 3969 amino acids in a complex structure. This protein is widely expressed in the developing embryo, where it functions as a regulator of nuclear transcription. In adult tissues, the protein is only minimally expressed [38,41,46,47].

The MLL protein is normally cleaved in the cytoplasm by caspasa 1 at amino acids 2666 (cleavable site 1 or CS1) and 2718 (cleavable site 2 or CS2), generating two subunits: the 300-kDa MLL-N and the 180-kDa MLL-C. MLL functions to acetylate, deacetylate and methylate the histones of nucleosomes [40,46]. The mature protein contains a 8.3-kb breakpoint cluster region between exons 5 and 11, and multiple protein domains have been identified: AT hooks, a DNA methyltransferase domain (transcriptional repression domain, TRD), a Plant homology domain (PHD), a transcription activator domain (TA) and Su (var) 3-9 enhancer of zest trithorax (SET) domain [38,47,48].

MLL gene alterations include deletions, duplications, inversions and reciprocal translocations. In reciprocal translocations, the fusion proteins are generated by interactions with the C-termini of other genes to replace the transcriptional repression and nuclear signaling domains located at the N-terminus of the MLL protein [49,50].

These fusion proteins have been postulated to be involved in leukemogenesis by increasing the expression of the HOXA9 gene during embryo development. The HOXA9 gene encodes a transcription factor, and the increased expression of this gene could represent a critical mechanism for MLL-related leukemia [46,49,51]. Another mechanism by which these fusion proteins promote leukemia is to increase the expression of FLT3 tyrosine kinase [41,52].

6. Prenatal origin

Numerous molecular biology studies have been conducted in twins with blood samples collected at birth from newborns (Guthrie cards) and with blood samples from the umbilical cord to detect inborn metabolic problems and other problems that could occur in newborns. Neonatal blood samples are stored, and thereafter the samples of a child with a diagnosis of leukemia are examined to understand the patient's genetic abnormalities at birth. These abnormalities are compared with those reported in the diagnosis of the patient. In a large proportion of neonatal blood samples, studies have concluded that the leukemia likely started *in utero* during fetal hematopoiesis, although this is not true for all chromosomal abnormalities [14,53,54].

Monozygotic and dizygotic twins have also been studied to determine the heritable fraction of childhood leukemia. More than 50% of twins share a placenta (monozygotic), which allows blood exchange. In these cases, it is likely that if one of the twins had a leukemic clone, it may have an intraplacentarian metastasis through which the clone could be transmitted to the other twin [37,53]. This hypothesis has been demonstrated through studies in twins with leukemia using translocation markers for unique genetic breakpoints, especially in TEL-AML1 and MLL rearrangements [14,53-55].

In twin infants with a diagnosis of leukemia, the concordance rate was approximately 100% among those twins who shared the placenta [53]. An explanation for this is that the MLL gene is sufficient to cause leukemia, which could happen if the protein has an overall effect on the structure of chromatin or on the stability of gene expression [37,56]. It is likely that the effect

of the MLL gene in DNA repair or cell cycle regulation facilitates additional genetic changes caused by continuous exposure to genotoxic chemicals *in utero* [14]. However, some authors have noted that the MLL gene is not sufficient to generate leukemogenesis and that additional secondary genetic events are necessary in the development of the disease [57,58]. More so when it has reported the presence of this rearrangement in children over 1 year of age which raises the possibility that the relation of this rearrangement to the development of ALL is similar to that of the TEL-AML1 rearrangement; that is, it is an essential cause, but it is indispensable that another environmental factor be involved in order for children with this rearrangement (acquired at birth or not) to develop the disease [59].

Unlike infant leukemias, acute leukemias in older children exhibit a concordance rate between identical twins who share the same placenta of only 10%. This finding, together with transgenic models, indicates that post-natal events are necessary to produce sufficient genetic changes to develop leukemia. This finding explains why leukemia in infants is a different entity than that of older children, and attention must be paid to transplacental exposure *in utero* during embryonic development and fetal hematopoiesis [37,60].

7. Enzyme DNA topoisomerase II

The function of the enzyme DNA topoisomerase II (DNAt2) is to relax the DNA strands that are tightened and knotted during cell replication [61]. DNAt2 generates a break in the double strands of DNA that are then re-sealed, causing a relaxation of the DNA. Some drugs used in the treatment of leukemia, such as the epidofilotoxinas and anthracyclines, have apoptotic effects by inhibiting DNAt2. These drugs interfere with the normal function of DNAt2 by stabilizing the break-cleavable complex, which is the DNAt2 enzyme complex responsible for breaking the double-stranded DNA, slowing the ligation of the strands and leaving free the single-stranded DNA ends that can lead to chromosomal abnormalities. These chromosomal abnormalities have been observed in leukemias secondary to the treatment of epidofilotoxins and anthracyclines in children and adults [62,63], and patients treated with these drugs have a greater likelihood of developing secondary AML with MLL translocations [64]. Several chemical compounds are able to inhibit DNAt2, including chemotherapeutic drugs containing quinone substances [65,66]. The enzyme NAD(P)h:quinone oxidoreductase 1 (NQO1) is involved in the metabolism of chemicals that inhibit DNAt2. The functional polymorphism C609T reduces the activity of NQO1 and exhibits a phenotypic dose-gene effect [67,68]. Several studies have assessed the associated risk of possessing the variant allele T at locus NQO1 C609T in patients with childhood AL and MLL rearrangement. The results are mixed; only some studies observed an increased risk with NQO1 C609T in infants with leukemia and MLL [66,69,70].

However, there are other sources of exposure to DNAt2 inhibitors that may increase the risk of acute leukemia in infants [42]. These DNAt2 inhibitors are found in some drugs, substances derived from benzene and naturally in some foods that contain flavonoids [71].

8. Therapy-related secondary leukemias

The growing use of intensive therapies in the treatment of patients with cancer has caused an increase in the incidence of secondary neoplasms. The complexity of anti-cancer treatments makes it difficult to know what agents are more leucemogenous and which act more quickly in the leukemic transformation of the hematopoiesis progenitor cells. The term secondary leukemia is usually employed to indicate both forms of AML evolving from previous myelodysplasia and forms of acute leukemia developing after exposure to environmental or therapeutic toxins or radiation (therapy-related). Secondary leukemias account for 10-30% of all AML. The majority of secondary leukemias resulting from the use of cytotoxic drugs can be divided into two well defined groups depending on whether the patient has received: 1) alkylating agents or 2) drugs binding to the enzyme DNA-topoisomerase II.

Alkylating agents related leukemias are very similar to post myelodysplasia leukemias being characterized frequently by a preleukemic phase, trilineage dysplasia, frequent cytogenetic abnormalities involving chromosomes 5 and 7 and a poor prognosis. Secondary leukemias related to therapy with topoisomerase II inhibitors are not preceded by a preleukemic phase and show frequently balanced translocations involving chromosome 11q23. Among therapy-related leukemias, AML is generally a second neoplasm, thus a predisposition to malignancy, independently from previous chemotherapy, cannot be excluded. It has been mentioned that the incidence of secondary leukemias increases with age [72] and leukemic cells predominantly exhibit a monocytic or myelomonocytic phenotype and balanced chromosomal translocations including 11q23 and 21q22 rearrangements or abnormalities such as t(15;17)(q22;q12) and inv(16)(p13q22). A history of previous treatment with topoisomerase-II-inhibitors is common in these individuals. However, as many patients have received multiple lines of treatment including several classes of chemotherapy compounds, both structural and balanced chromosomal aberrations are frequently observed in the leukaemic clone. The World Health Organization (WHO) has therefore abandoned its former classification into alkylating agent or topoisomerase-II-inhibitor associated therapy-related disease. As a conservative estimate, about 10% of cases of AML and myelodysplastic syndrome (MDS) are therapy related [73].

Alkylating agents

Alkylating agents were the first chemotherapeutic compounds to be associated with leukaemia development after successful treatment of solid and haematological cancers [74-78]. They comprise a large group of anti-cancer drugs with clinical application across almost all cancer types. Alkylating agents induce DNA damage by transferring alkyl groups – such as -CH3 or -CH2-CH3 – to oxygen or nitrogen atoms of DNA bases, resulting in highly mutagenic DNA base lesions, such as O6-methylguanine and N3-methylcytosine [79-82].

Drugs binding to the enzyme DNA-topoisomerase II (topoisomerase inhibitors)

While alkylating agents associated with therapy-related myeloid neoplasms (t-MNs) are characterized by a complex karyotype often featuring partial or complete loss of chromo-

somes 5 and/or 7, exposure to topoisomerase inhibitors leads to the development of leukaemias with balanced translocations involving MLL at 11q23, RUNX1 at 21q22 and RARA at 17q21 [83-85]. MLL fusion genes are also MLL fusion genes are also common in secondary acute myeloid leukemia (usually French-American-British (FAB) M4/M5) associated with prior therapeutic exposure to topoisomerase-II inhibiting anthracyclines or epidophyllotoxins [62]. These observations have prompted speculation on possible exposure to topoisomerase-II inhibiting substances during pregnancy that might give rise to MLL fusions during fetal hematopoiesis [86].

DNA topoisomerases are critical enzymes responsible for unknotting and relaxing supercoiled DNA, thus allowing DNA replication to occur. To relax supercoiled DNA, topoisomerases bind covalently to the DNA strand and create transient single (type I topoisomerases) and DSBs (type II topoisomerases). These DNA strand breaks are readily religated after topoisomerases are released from the DNA [87]. As these ubiquitous enzymes are essential to cell survival, DNA topoisomerases have become a valuable target for several cytostatic drugs, such as epipodophyllotoxins and anthracyclines. Topoisomerase inhibitors block the release of topoisomerases from cleaved DNA, preventing religation of the DNA strands [88]. Thus, topoisomerase inhibitors lead to the generation of permanent DNA DSBs that trigger DSB-induced apoptosis. However, persistent DNA DSBs are also highly mutagenic and can result in chromosomal deletions, insertions, inversions and translocations, all of which are characteristic of the leukaemic cell clone in t-MNs. The exact molecular effects of these inhibitors on the acquisition of chromosomal aberrations and the development of this t-MN subtype have recently been reviewed in detail [89].

Dexrazoxane – a bisdioxopiperazine iron chelator used to reduce cardiopulmonary toxicity in patients treated with anthracyclines – also interferes with topoisomerase II in its dimerized state by bridging and stabilizing the ATPase region. In a randomized phase III study in paediatric patients treated with chemo- and radiotherapy for Hodgkin´s disease, dexrazoxane was associated with a cumulative incidence of MDS/AML of 2.5% - 1.0% as compared with 0.85% - 0.6% for the non-dexrazoxane group (P = 0.16). This trend towards an increased risk of secondary neoplasms associated with dexrazoxane was subsequently confirmed in patients with childhood acute lymphoblastic leukaemia [90]. In children cured of ALL, the risk of a therapy-related acute myeloid leukaemia (t-AML) has been evaluated in different series to be between 3.8% at 6 years and 5.9% at 4 years [64,91-96]. The risk of secondary acute myeloid leukemia (sAML) was higher among ALL children who received a high cumulative dose of epipodophyllotoxins (>4,000 mg/m2) and prolonged epipodophyllotoxin therapy in weekly or twice-weekly doses. In adults a GIMEMA study demonstrated a low incidence of t-AML, which could be explained by the lower doses of epipodophyllotoxins administered in the various therapeutic approaches used for the treatment of adult ALL [96].

MLL gene has been involved in secondary leukemias treatment, mainly of the type AML in patients treated with inhibitors of topoisomerase II as a primary cancer treatment. It has been postulated the presence of similar mechanisms for Leukemia in infants whose mothers had exposure to native II topoisomerases [97].

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9. Diet and infant leukemia

Studies on environmental risk factors related to AL with MLL rearrangements have focused on maternal diet effects on *in utero* exposure. Dietary compounds exists that can inhibit the function of DNAt2, thereby posing a potential leukemogenesis threat in infants [43,64]. DNAt2 is critical in cellular processes such as replication, where transiently breaks down and subsequently seals the DNA strand [37]. DNAt2 is able to rapidly increase its activity during cell division [98]. Diet is a natural source of DNAt2 inhibitors, including flavonoids [71,99].

Flavonoids are a very large group of Polyphenolic compounds found in foods of plant origin. Polyphenols are involved in the development and reproduction of plants, and they provide resistance against pathogens, plagues and protect crops from diseases that inhibit the germination of their seeds [100]. Flavonoids are divided into 6 subgroups: flavones, flavanols, flavanones, catechins, anthocyanidins and isoflavones [71] (see table 2); in the last decade, more than 5000 subclasses have been identified [101,102]. Importantly, several biological effects have been observed in in vitro studies of flavonoids, including its antioxidant activity, modulation of enzyme activity, inhibition cell proliferation and use as antibiotics, anti-allergy, anti-diarrhea, anti-ulcer and anti-inflammatory agents [103-106].

The properties attributed to flavonoids have prompted increased interest in alternative medicine and herbal remedies. Numerous foods, beverages and supplements exist on the market that contains high levels of flavonoids. Therefore, it is likely that the amount of flavonoids in the typical diet is presently increasing [102].

The study the consumption of DNAt2 inhibitors during pregnancy in women who have children who develop leukemia is founded on the idea that foods containing natural DNAt2 inhibitors cause damage to DNA, much in the same way as the epidofilotoxinas. There have been several bioavailability studies on flavonoids that have demonstrated that there are differences in their absorption, depending on the source of food. The accumulation of these compounds in blood has been measured [107]. Some studies in animals and in vitro have demonstrated that flavonoid DNAt2 inhibitors are capable of crossing the placenta and damaging DNA [108,109]. One study reported the flavonoids can cause a break in the MLL gene in hematopoietic progenitor cells, which was reversible when the exposure was removed. The site of disruption caused by the flavonoids was co-localized with the same site associated with the epidofilotoxinas [37,60,99]. All of these findings provide evidence for epidemiological studies in the pursuit of this association with leukemia in infants.

Studies of maternal diets during pregnancy and their association with childhood AL have been led by Ross JA. [110], who through a case-control study in infants and a questionnaire for maternal exposure to dietary DNAt2 inhibitors and drugs in pregnancy observed a statistically significant association between AML and the medium and high consumption of DNAt2 inhibitors (OR 9.8; 95% confidence interval [CI] 1.1-84.8; OR 10.2; 95% CI 1.1-96.4). However, this study observed no association with ALL. Ross JA intends to continue studying infants with AL and stresses the importance of incorporating molecular markers that could provide more information.

Flavones (Apigenin, luteolin, diosmetin)	Flavonols (Quercetin, myrecetin, kaempferol)	Flavanones (Naringenin, hesperidin)	Catechins or Flavanols (Epicatechin, gallocatechin)	Anthocyanidins (Pelargonidin, malvidin, cyanidin)	Isoflavones (Genistein, daidzein)
Parsley	Onions	Citrus foods	Tea	Cherries	Soya beans
Thyme	Kale	Prunes	Apples	Grapes	Legumes
Celery	Broccoli		Cocoa		
Sweet red	Apples				
pepper	Cherries				
	Fennel				
	Sorrel				
	Berries				
	Tea				

Table 2. Major subgroups of flavonoids and food sources.

Later, Jensen CD et al. [111] studied maternal diet and its association with childhood ALL through a food frequency questionnaire, observing a protective effect with the consumption of vegetables, protein and fruits (OR 0.53; 95% CI 0.33-0.85; OR 0.40; 95% CI 0.18-0.90; OR 0.71; 95% CI 0.49-1.04, respectively). In 2005s Spector et al. [34] published the results of a case-control study in infants in which they proposed that exposure to high levels of DNAt2 inhibitors in the diet was associated with the risk of MLL+ leukemia in infants. The authors observed a non-significant association between MLL+ AML but a trend among the second and fourth quartiles of DNAt2 inhibitor consumption (OR 1.9; 95% CI 0.5-7.0; OR 2.1; 95% CI 0.6-7.7; OR 3.2; 95% CI 0.9-11.9). A non-significant inverse association was observed with MLL+ ALL. Another study conducted by Petridou et al. [112] in children ≤4 years old diagnosed with ALL asked about the mothers' diets during pregnancy and found that the consumption of fruits (OR 0.72; 95% CI 0.57-0.91), vegetables (OR 0.76; 95% CI 0.60-09) and fish/seafood (OR 0.72; 95% CI 0.59-0.89) decreased the risk for ALL. However, the consumption of sugar/honey and meat/derivatives increased the risk for ALL (OR 1.32; 95% CI 1.05-1.67; OR 1.25; 95% CI 1.00-1.57, respectively). The most recent study on maternal diet and childhood ALL was undertaken by Kwan ML et al., [113] who applied a food-frequency questionnaire about food consumed 1 year before pregnancy. The results of their study indicate that the risk for ALL was inversely associated with maternal consumption of vegetables (OR 0.65; 95% CI 0.50-0.84), sources of protein (OR 0.55; 95% CI 0.32-0.96), fruits (OR 0.81; 95% CI 0.65-1.00) and legume food groups (OR 0.75; 95% CI 0.59-0.95).

Thus far, epidemiological studies have identified the protective effect of fruits and vegetables consumption during pregnancy against infantile ALL. These results are not observed in AML with the exception of the studies of Ross et al., in which the authors identified a positive association between the high intake of DNAt2 inhibitors in foods and AML/MLL+ in infants. These results confirm that AL in children is composed of different subgroups with different disease etiologies [37,42].

The most recent epidemiological study in infants is the one published by the group of Ross et al., [114] with a significant number of cases (374). In this study, the authors describe some of the demographic factors and the MLL gene status in infants with leukemia. They generally reported a higher frequency of females (50.8%), and the most common ethnic group was Caucasian (70%), followed by Hispanics (27.8%). The most frequent age of diagnosis was 4-6 months (27.8%), and 51.5% of cases were MLL+, 33.0% were MLL-, and 15.6% were undetermined. The chromosome most frequently found fused to the MLL gene was chromosome 4 [t (4; 11)]. Interestingly, the black ethnic group had a lower risk of MLL+ leukemia (OR 0.27; 95% CI 0.11-0.70), and a protective effect was observed in infants 10-12 months old (OR 0.39; 95% CI 0.21-0.73). Cases of ALL and t(9;11) were diagnosed at older ages than cases with t(4;11) or other translocations (P = 0.01). These findings provide important information of the biology of the disease. Undoubtedly, this study necessitates future publications to report socio-economic data, exposure to DNAt2 inhibitors and other maternal risk factors during pregnancy and their association with leukemia in infants.

Another study is currently being conducted by our research group in Mexico City. This study emerged because Mexico City has a high incidence rate of acute leukemia in infants. In addition, a previous study observed that the frequency of MLL/AF4 rearrangements in patients diagnosed with childhood leukemia was high [59]. This is an epidemiological case-control study in infants; the objectives are to identify the relationship between *in utero* exposure to environmental factors inhibiting DNAt2 that are present in the maternal diet during pregnancy, including drugs and benzene derivatives. Biological samples of patients are being analyzed to detect the MLL/AF4 gene rearrangement in infants. In addition, we will know the frequencies of exposure to environmental factors that inhibit DNAt2 in the mothers of infants with MLL+ AL. Nine hospitals that belong to the most important public health institutions in our country are participating in this study. These hospitals diagnose and treat 97.5% of all leukemia cases in Mexico City [7]. The results obtained from this study will be very relevant to one of the cities with the highest incidence rates for childhood AL.

10. Future directions

Due to the findings reported thus far, the authors have recommended carrying out studies in infants that are focused on different biological strata like female/male rations because hormonal differences could indicate an important predisposition to the presence of MLL+ rearrangement. Another suggestion is to study different ethnic groups, where the genetic involvement can provide substantial information about this cohort [112]. For future studies, one must

consider the importance of a big sample size, questionnaires validated and, when possible to incorporate biological or environmental samples that enhance the exposure information, such as pre-diagnostic biological samples. In addition to considering collaborative studies between epidemiologists, clinicians, biologists, and others will enrich the results of these studies.

11. Conclusion

There is sufficient evidence to indicate that acute leukemia in infants is initiated *in utero* with MLL rearrangements. Epidemiological studies have demonstrated that flavonoids and some benzene derivatives present in the maternal diet during pregnancy can act as inhibitors of DNAt2 and are associated with the development of AML in infants with MLL+. This association has not been observed for ALL in infants, although an inverse association with the consumption of vegetables and fruits has been reported for ALL. Is a priority to identify environmental or other types of factors that could be contributing to the greater presence of this type of rearrangement during pregnancy and their association with leukemia in infants.

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