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Survival of Patients with Acute Lymphoblastic Leukemia

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1. Introduction

Over the past 50 years, the treatment of patients with acute lymphoblastic leukemia (ALL) has significantly improved. This success is measured by the improved survival of ALL patients from less than 10% in the 1960s to more than 80% in more recent reports. However, many factors influence to a good outcome to treatment and subsequently in the improved survival of patients with ALL.

Age is the factor that has been more associated with survival. Younger patients (especially those younger than age 50) have a better survival than older patients. Not only age but also gender and race also are related with survival of ALL patients. The girls have showed a better survival than boys, this partly due to boys' risks for testicular cancer. African-American and Hispanic Individuals have lower survival rates than Caucasian and Asian individual, but this may be due to poorer access to treatment. A very important factor in the clinic that somehow predicts good to bad prognosis of the patient and of course has also been linked to survival is the Initial white blood cell (WBC) count; people diagnosed with a WBC count below 50,000/ μ L tend to be better than people with higher WBC counts. Even, ALL subtype plays a role very important. For example, patients with T-cell ALL tend to have a better prognosis and survival than those with mature B-cell ALL (Burkitt leukemia). Nowadays, the identification of chromosome translocations help to prognosis of ALL patients; people who have Philadelphia chromosome-positive ALL tend to have a poorer prognosis, although is important to note that new treatments are helping many of these patients achieve remission.

Effectively, all the above factors (age, gender, race, Initial white blood cell (WBC) count, ALL subtype, and chromosome translocations) have an impact on treatment and survival of patients with leukemia. Since several years it is known that single nucleotide polymorphisms (SNPs) are some of the population genetic variations that greatly influence in the response to treatment of patients with ALL. It has been shown to SNPs modify the metabolism of chemical agents used in chemotherapy by affect the normal activity of enzymes involved in drug metabolism. This speaks of a very important role of these SNPs in the adequately outcome and survival of patients with ALL under treatment. This chapter shows how all the above factors play an important role in the survival to ALL and as the survival of patients with ALL varies according to these factors in different populations. The challenge remains to optimize the treatments according to population groups.

2. Age

Survival rates for children with ALL have increased dramatically over the past 4 decades, with 5-year survival rates of >90% in recent trials [1]. Data emerging from the surveillance, epidemiology and end results (SEER) database suggest that patients' age serves as a significant prognostic factor that affects clinical outcomes such as overall survival (OS) [2]. The SEER 9 (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah) showed that the 5-year survival rates for children younger than age 15 years with ALL improved from 61.0% in 1975-1978 to 88.5% in 1999-2002. Adolescents 15 to 19 years of age also showed improvement in survival over the same period, although their outcome in recent periods (50.1% 5-year survival in 1999-2002) was lower than that among children younger than age 15 years [3]. This lower survival rate partially reflects differences in tumor biology between children and older adolescents and likely also reflects differences in the way medical oncologists and pediatric oncologists have historically treated ALL arising in this age group [4, 5]. Survival for infants remains poor compared with that for children 1 to 14 years of age, although 5-year survival rates have increased from 22% in 1975-1978 to 62% in 1999-2002 [3].

In 2005, estimates derived SEER program of the National Cancer Institute placed the number of survivors of childhood ALL in the United States at 49 271 (0-19 years of age) being one of the cancer types with the largest number of survivors to 5-years. However, survival decreased with increasing age, with a relatively notable decline in survival beginning at ages 20 o more years [6]. As in Japanese population of aged 15-60 years where survival at 5 years is 35.0% [7] and Japanese children younger than 16 years age had 7-year OS rate of 76.0% [8]. In work done at Department of Epidemiology and Cancer Control, St Jude Children's Research Hospital, Memphis, TN of 1991 to 2006 in children with acute lymphoblastic leukemia; 5-year event-free survival (EFS) estimates were 88% for children aged 1-9 years, 73% for adolescents aged 10-15 years, 69% for those older than 15 years, and 44% for babies younger than 12 months [9, 10]. Today, the long-term survival has increased from approximately 10% in the early- to mid-1960s to more than 90% at St Jude Children's Research Hospital, Memphis, TN [1].

In Italian children between 1 and 18 years of age with newly diagnosed of ALL, enrolled in the AIEOP-BFM ALL 2000 study, had a 7-year EFS and survival of 80.4% and 91.8%, respectively. However when the children were stratified by minimal residual disease (MRD) their overall 7-year estimates for EFS and survival were 80.7% and 92.8%, respectively [11]. In United Kingdom, children aged 1–18 years survival estimates at 5 years were 87% [12]. In Pakistani population aged > 15 years their median survival was 12.7 months and disease-free survival was 6.2 months [13].

Currently, due to intensive chemotherapy regimens, the outcome of adult ALL has improved markedly. The complete response rates now are more than 80% [14] and the long-term survival rate is 30%–45% [15]. Based on a study by Stephen Hunger and colleagues, 5-year OS rates now above 90% for the first time (83.7% in the period 1990-1994; 90.4% in the most recent period 2000-2005). This study is based on information on 21,626 ALL patients between 0 and 22 years who were enrolled onto the Children's Oncology Group (COG) ALL clinical trials from 1990 to 2005. It is clear that survival improved in all subgroups of ALL (1-9 years), except for infants under the age of 1 year. Besides, 5-year OS also remains significantly lower (81.6%) for children over the age of 10 years [16]. Childhood ALL reflects one of the diagnosis for which the most impressive improvements have been realized [1].

The better results seen among the childhood population as compared to adults with ALL have been attributed to a number of prognostic factors. It is important to consider a number of important differences between younger and older patients with ALL exist. First, the biology of both, underlying disease and the patients' metabolic changes with age are very different between two cohorts [17]. The second major difference is the difference in therapy related toxicity [18]. The third potential cause for a superior outcome in the younger population is relates to the protocols administered. It is important to consider that the treatment protocols from each institution, the dose adjustments and many others factors can increase long-term survival, but the factor toxicity could have a negative effect on long-term.

3. Gender

Survival disparity by the sex of the patient with leukemia has been observed since the nineteen sixties; however, what remains to be fully grasped are the factors responsible for this persisting survival difference between boys and girls. Girls continue to demonstrate survival advantage relative to boys. Studies over the past years have repeatedly shown that after diagnosis of pediatric leukemia, boys present with poorer survival than the girls (Table 2).

In 2012 using a large sample and long-term data could help explain the ongoing variance in leukemia survival comparing boys to girls and found that boys are more likely to die from leukemia (Table 1). The explanation to the observed disparity in survival by sex, since most of the patients who had T-cell type were boys, and survival was poorer among boys in this study [19]. A biological explanation for sex disparity in leukemia survival, it is plausible to suspect XY chromosomal instability as a possible contribution to abnormal cellular proliferation, thus resulting in a biologically aggressive leukemia among male patients. Also, it

might be possible that testosterone or estrogen may play a small role in pediatric leukemia, this partly due to boys’ risks for develop testicular cancer [19].

Population			Survival estimated	% of Overall Survival	Number of patients	Ref.
Sex						
U.S.	Male	Children	At 5 years	53.9	8,622	[19]
	Female			58.0	6,593	
European	Male	Children	At 5 years	63.0	401	[20]
	Female			67.0	299	
U.S.	Male	Children	At 5 years	63.5	1,151	[21]
	Female			73.4	904	
WBC count						
Japanese	< 10.0x10 ⁹ /L	Children	At 7 years	71.5	300	[22]
	10.0-49.9x10 ⁹ /L			62.7	206	
	50.0-99.9x10 ⁹ /L			52.9	35	
	≥100.0x10 ⁹ /L			19.3	48	
Japanese	<3x10 ⁹ /L	Adults	At 5 years	20.0	15	[23]
	3x10 ⁹ -50x10 ⁹ /L			48.8	45	
	>50x10 ⁹ /L			19.2	27	
Korean	<100.0x10 ³ /μL	Children	At 4 years	87.5	83	[24]
	≥100.0x10 ³ /μL			57.1	17	
European	<50x10 ⁹ /L	Children	At 5 years	92.3	1,348	[11]
	50.0-99.9x10 ⁹ /L			77.6	1,647	
	≥100.0x10 ⁹ /L			50.1	189	
European	<50x10 ⁹ /L	Children	At 5 years	94.0	923	[12]
	>50x10 ⁹ /L			61.0	166	
U.S.	<50,000/μL	Children	At 4 years	80.3	68	[25]

Table 1. Recent studies on survival of ALL patients by gender and Initial white blood cell (WBC) count

4. Initial White Blood Cell (WBC) count

Along with age, the initial peripheral blood leukocyte count is another of the firsts identified prognostic factors in every study of ALL. The WBC at diagnosis is a crucial variable for describing the nature of the patient’s leukemia and especially the tumor burden. The other measures of the tumor burden are the size of a mediastinal mass, hepatosplenomegaly, and enlargement of lymph nodes. Children with WBC of more than 50x10⁹/L are commonly considered to be at high risk of relapse and receive intensive treatment [1, 2]. In retrospective analysis was found that patients with hyperleukocytosis (WBC count

>50 $10^9/L$) were significantly related to lower survival. Similar findings are the rule in reports from various study groups (Table 1).

The cytogenetic features are closely linked to the WBC and at least partly explain the prognostic of WBC, although there is evidence that children with similar cytogenetic aberrations may have very different WBCs, and their prognostic value is related partly to the WBC [26-28].

Race/ethnicity		Survival estimated	% of Overall Survival	Number of patients	Ref.
Non-Hispanic white			70	1,529	
Hispanic			56	178	
Asian/Pacific islander	Children	At 5 years	56	2,542	[29]
Non-Hispanic black			46	408	
Whites			78	6703	
Blacks			65	506	
Hispanics	Children	At 5 years	69	1071	[30]
Asians			84	167	
Whites			70	3621	
Blacks			57	356	
Asians	Children	At 5 years	71	410	[31]
Native American			54	61	
Hispanics			63	504	

Table 2. Recent studies on survival of ALL patients by race/ethnicity

5. Race/ethnicity

Variability in survival outcome across racial and ethnic groups (hereafter referred to as race/ethnicity) also has been identified in some, but not all, clinical research. Survival rates in Black, Hispanic and Native American children with ALL have been somewhat lower than the rates in White children with ALL (Table 2). This difference may be therapy-dependent [32]. Asian children with ALL fare slightly better than white children [33]. The reason for better outcome in White and Asian children compared with Black, Native American and Hispanic children is at least partially explained by the different spectrum of ALL subtypes. For example, blacks have a higher incidence of T-cell ALL and lower rates of favorable genetic subtypes of ALL. However, these differences do not completely explain the observed racial differences in outcome [33].

Population		Survival estimated	% of Overall Survival	Number of patients	Ref.
<i>ETV6-RUNX1 [t(12;21)]</i>					
Brazilian	Children	At 5 years	77.6	58	[34]
Nordic countries	Children	At 5 years	65.0	669	[35]
U.S.	Children	At 5 years	93.7	662	[36]
French	Children	At 5 years	50.0	73	[37]
<i>BCR-ABL [t(9;22)]</i>					
Spanish	Adults	At 4 years	16.0	30	[38]
Europe and U.S.	Children	At 2 years	35.5 - 46.3	267	[39]
U.S.	Children	At 4 years	35.0	120	[40]
Japanese	Adults	At 2 years	12.5	80	[41]
<i>MLL-AF4[t(4;11) (q21;q23)]</i>					
Europe	Adults	At 5 years	39.0	236	[42]
Japanese	Infants	At 3 years	43.5	54	[43]
Europe	Adults	At 5 years	13.0	24	[44]
Spanish	Infants, Children, Adults	At 5 years	36.0	51	[45]
<i>PBX1/E2A[t(1;19)(q23;p13.3)/der(19)t(1;19)(q23;p13.3)]</i>					
Caucasian	Children	At 5 years	90.0	31	[46]
U.S.	Children	At 5 years	84.2	41	[47]
Europe	Children	At 5 years	84.0	50	[12]
Europe	Adults	At 5 years	79.0	47	[48]

Table 3. Studies on survival of ALL patients with genetic rearrangements

6. Survival by ALL Immunophenotype

The World Health Organization (WHO) classifies ALL as either B lymphoblastic leukemia or T lymphoblastic leukemia [49]. Historically, T-cell ALL patients have had a worse prognosis than other ALL, the relapse rate of T-cell ALL is greater than B-cell ALL cases, and T-cell ALL cases have shown less EFS than B-ALL cases [50, 51]. Patients with T-cell ALL treated on Dana-Farber Cancer Institute (DFCI) Boston, MA had an overall survival at 5 years of 78 % compared with 86 % for B progenitor ALL patients [50]. A study based cancer registry areas of the Surveillance, Epidemiology and End Results (SEER) Program (SEER-17) during 2001 to 2007 reported that infants with B-cell ALL and ALL of unknown lineage had intermediate survival to 5-years compared with 5- to 19-year and 20- to 39-year age groups.

Notably, children and young adults 1 to 4 and 5 to 19 years of age with B-cell ALL had more favorable survival (Approximately 99% and 88%) than those with T-cell ALL (Approximately 84% and 78%). In contrast, survival for T-cell ALL was substantially higher than B-cell ALL among adults 20 to 39, 40 to 59, and 60 years or older of age [52].

7. Chromosomal translocations in B-cell acute lymphoblastic leukemia (B-cell ALL)

Acute lymphoblastic leukemia is a heterogeneous disease that originates from lymphocyte progenitor cells of B- or T-cell origin. ALL comprises multiple distinct subtypes that are characterized by recurrent copy number alterations and structural chromosomal rearrangements, which have important clinical implications. Such cytogenetically distinct subtypes include B-cell precursor (BCP) leukemia with the chromosomal translocations t(12;21)(p13;q22) [ETV6/RUNX1], t(9;22)(q11;q34) [BCR/ABL1], (4;11)(q21;q23)/MLL-AF4, t(11;19)/MLL-ENL, t(1;19)(q23;p13)/PBX1/E2A karyotypes. It is well established that ALL subtypes differ from a clinical perspective, but the underlying molecular consequences of most of the recurrent chromosomal abnormalities are poorly understood [53].

8. ETV6-RUNX1 [t(12;21) cryptic translocation, formerly known as TEL-AML1]

The translocation t(12;21)(p13;q22) is the most frequent chromosomal alteration in childhood B-lineage ALL (B-ALL) [54], which involves the fusion of the ETV6 (alias TEL) gene on chromosome 12 to the RUNX1 gene on chromosome 21. It is identified in 20% to 25% of the cases of B-precursor ALL and is rarely observed in T-lineage ALL [55]. The t(12;21) is most commonly found in children aged 2 to 9 years [56]. Reports generally indicate favorable OS in children with the ETV6-RUNX1 fusion (Table 3); however, the prognostic impact of this genetic feature is modified by factors such as early response to treatment and treatment regimen [57].

9. Philadelphia chromosome (Ph) or t(9;22) translocation

The Ph results from a reciprocal translocation (t) between chromosomes 9 and 22 (t [9;22] [q34;q11]) [58, 59], occurs in approximately 3 to 5% of children, as compared with up to 30 percent of adults with ALL [60, 61].

The Ph produces a fusion gene on chromosome 22, namely, the breakpoint cluster region Abelson leukemia viral proto-oncogene (BCR-ABL). The translocation can result in 3 fusion protein of different sizes: p190, p210, and p230 [62]. The p190 BCR-ABL fusion gene occurs in about 90% of children with Ph-positive ALL [63] and between 50% and 80% of adults with Ph-positive ALL [64, 65].

Ph-positive ALL has an extremely poor prognosis overall (rates of EFS are 30 to 46 percent in children and less than 20 percent in adults) Table 3. However, some investigators suggest that in this type of ALL, the prognosis is influenced by the treatment with glucocorticoids (and intrathecal methotrexate) [66], or by other factors (such as age and leukocyte count at diagnosis) [67, 68]. These variations in the response to therapy suggest that Ph-positive ALL is heterogeneous with regard to sensitivity to treatment [39].

10. MLL translocations

10.1. MLL-AF4; t(4;11) (q21;q23) translocation

The incidence of t(4;11)(q21;q23)/MLL-AF4, occurring in over 50% ALL cases in infants aged less than 6 months, in 10–20% of older infants, in about 2% of children, and in almost 10% of adults [69, 70]. The presence of the translocation t(4;11)(q21;q23) or a fusion gene MLL-AF4 is detected in almost 10% of newly diagnosed B-cell ALL and in about 30–40% of pro-B ALL subtypes [71, 72].

A t(4;11)(q21;q23)/MLL-AF4 positive ALL is generally considered as a high risk leukemia, characterized by a poor clinical outcome respect to other cytogenetic risk groups [73]. Moreover, in several studies it has been demonstrated that cytogenetic-molecular risk and WBC count at diagnosis were the main prognostic factors that influenced OS in ALL patients (Table 3).

10.2. MLL-ENL; t(11;19) translocation

The t(11;19)/ MLL-ENL is present in approximately 1% of cases and occurs in both early B-cell and T-cell ALL [74]. Outcome for infants with t(11;19) is poor, but outcome appears relatively favorable in older children with T-cell ALL and the t(11;19) translocation [74].

10.3. PBX1/E2A; t(1;19)(q23;p13) translocation

The translocation t(1;19)(q23;p13), and its unbalanced variant del(19)t(1;19)(q23;p13), is a primary and well known chromosome abnormality in childhood B-cell precursor ALL, being present in 3–5% of all such cases [75, 76].

The t(1;19) produces a fusion between TCF3 gene on 19p13 and PBX1 on 1q23 [77], with the TCF3-PBX1 fusion transcript being expressed from the chromosome 19 [78]. Initially, t(1;19) was associated with a poor prognosis in ALL [79, 80], however most patients treated by contemporary therapies now achieve improved outcomes (Table 6).

11. Chromosomal translocations in T-cell acute lymphoblastic leukemia (T-cell ALL)

T-cell ALL accounts for about 15% and 25% of ALL in pediatric and adult cohorts respectively [69]. Cytogenetic abnormalities are rare in T-cell ALL. Multiple chromosomal translo-

cations have been identified in T-cell ALL, with many genes encoding for transcription factors (e.g., TAL1; [t(1;14)(p32;q11) and t(1;7)(p32;q34)], LMO1; [t(11;14)(p15;q11)], LMO2; [t(11;14)(p13;q11) and t(7;11)(q35;p13)], LYL1; [t(7;19)(q34;p13)], TLX1/HOX11 [t(7;10)(q34;q24) and t(10;14)(q24;q11)], and TLX3/HOX11L2 [t(5;14)(q35;q32)]) fusing to one of the T-cell receptor (TCR) loci and resulting in aberrant expression of these transcription factors in leukemia cells [81]. Historically, T-cell ALL in children has been associated with a worse prognosis than other sub-types of childhood ALL [82, 83].

High expression of TLX1/HOX11 resulting from translocations involving this gene occurs in 5% to 10% of pediatric T-cell ALL cases and is associated with more favorable outcome in both adults and children with T-cell ALL [84-86]. Overexpression of TLX3/HOX11L2 resulting from the t(5;14)(q35;q32) translocation occurs in approximately 20% of pediatric T-cell ALL cases and appears to be associated with increased risk of treatment failure [85].

12. Gene polymorphisms associated to poor survival in ALL patients

It is difficult to define which component of the protocol/regimen is the responsible for the improved outcome of patients with ALL. Antifolates, such as methotrexate (MTX), are competitive inhibitors of folate-dependent enzymes and are widely used in the treatment of many human cancers [87]. In last decades, the MTX has been a key agent for the treatment of ALL and the benefit of high-dose MTX is well established as it significantly increases cure rates and improves patients' prognosis [88]. MTX exerts its cytotoxic effects by competitively inhibiting dihydrofolate reductase (DHFR), the enzyme responsible for converting folates to tetrahydrofolate, the reduced folate carriers which function in the transfer of carbon units. These carbon units are required for de novo purine synthesis and the methylation of uracil to thymine in DNA synthesis [89].

MTX enters the cells and is metabolized into 7-hydroxymethotrexate (7-OHMTX), 2,4-diamino-N¹⁰-methylpteroic acid (DAMPA) and more active derivatives as methotrexate polyglutamates (MTXPG) with sequential gamma-linkage of 2 to 6 glutamyl residues by the folylpolyglutamate synthetase (FPGS) [88]. MTXPG retained in cells for a longer time result in prolonged MTX antifolate effect [89]. However, accumulation of MTXPG is a critical factor associated with cytotoxicity and response of ALL patients to the therapy [89]. On the other hand, the polyglutamation process competes with deconjugation that converts MTXPG back into MTX by gamma-glutamyl hydrolase (GGH). Long chain MTXPG have higher affinity than MTX for the enzymes involved in de novo purine synthesis such as 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC) and thymidilate synthase (TS), which results in a reinforcement of MTX inhibition (Figure 1) [88]. Thus, intracellular formation of MTXPG enhances the cytotoxic and antileukemic effect of MTX.

The disease-free survival of childhood ALL has improved steadily the last decades, reaching 80% in the developed countries [17]. Despite the advances, almost 20% of the children either relapse or do not respond to treatment. This seems to be related to various parameters, in-

cluding the presence of polymorphisms of drug transporters, receptors, targets, and drug-metabolizing enzymes, hence influencing the efficacy, the toxicity of therapy [91].

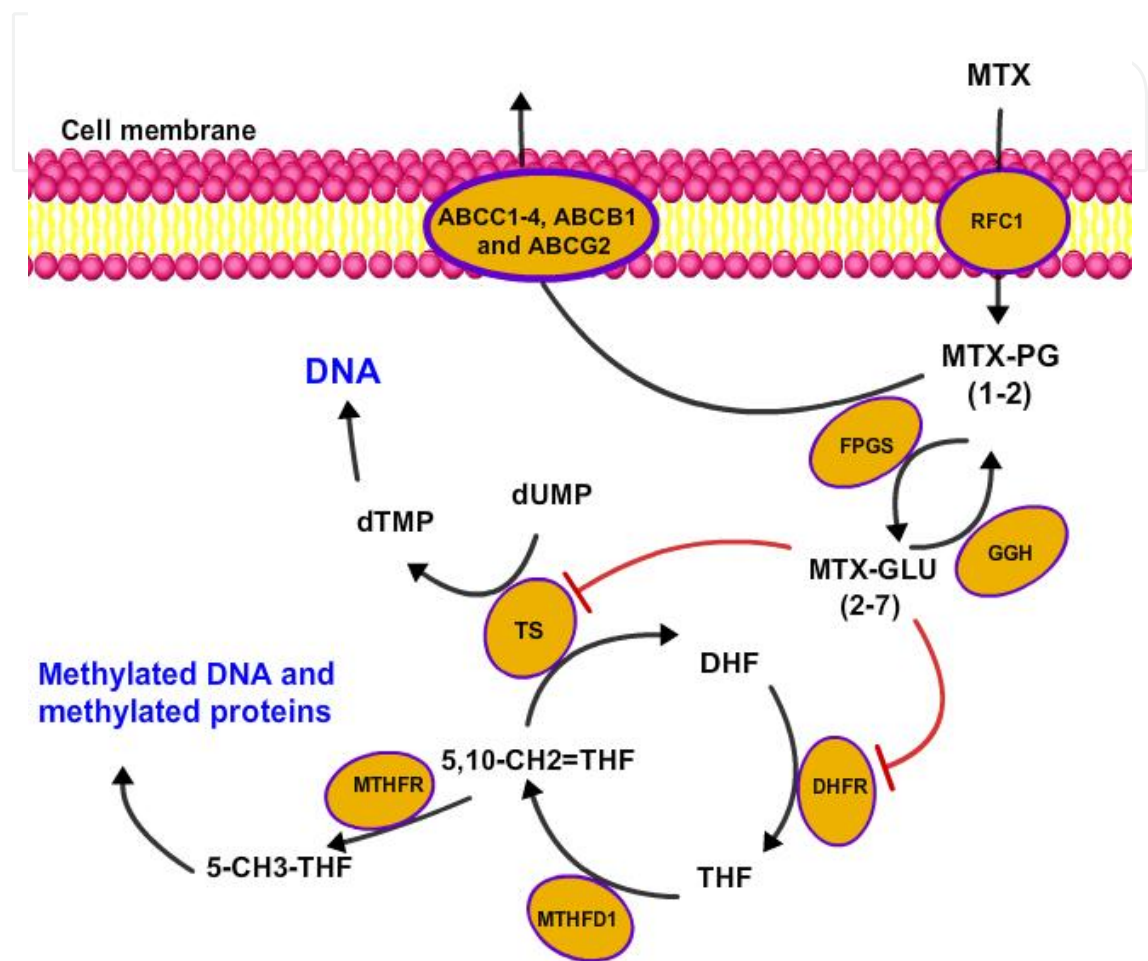


Figure 1. Methotrexate enters cells through the reduced folate carrier (RFC1) or other transport systems. Its main intracellular target is **dihydrofolate reductase (DHFR)**, inhibition of which results in accumulation of dihydrofolate (DHF) and depletion of cellular folates. Cytosolic **folylpolyglutamyl synthase (FPGS)** adds glutamate residues to methotrexate to produce methotrexate polyglutamates (MTXPGs), they are retained by the cell, and the resulting increase the efficacy of methotrexate. The addition of glutamate residues to methotrexate also increases its affinity for other target enzymes (**thymidylate synthetase (TS)** and **dihydrofolate reductase (DHFR)**). Other enzymes that are indirectly affected by methotrexate are **5,10-methylenetetrahydrofolate reductase (MTHFR)** and **methylenetetrahydrofolate dehydrogenase (MTHFD1)**. dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophosphate; THF, tetrahydrofolate. Figure modified with permission from Ref. [90] © PharmGKB and Stanford University (2011).

Recently, attention has been drawn on genes involved in diverse metabolic pathways, which are known to be polymorphic at various sites and can affect both the susceptibility for leukemia, the treatment outcome and survival in patients with ALL [91].

13. The reduced folate carrier (RFC1/SLC19A1)

Several polymorphisms in enzymes of the folate cycle as well as in the MTX transporters have been described. The reduced folate carrier gene (RFC1) is a major MTX transporter whose impaired function was recognized as a frequent mechanism of antifolate resistance [92]. The most common SNP in RFC1, 80A>G, which results in the amino acid substitution of Arg with His at position 27 of the RFC1 protein, may alter the affinity of the transporter [93]. Several investigators had studied the association of the SNP of RFC G80A and the outcome in ALL. Reports generally indicate association between the G/G and/or A/G genotypes of the G80A polymorphism with a poorer survival in patient's children and adults con ALL. Survival rates in Italian and Mexican population with ALL have been somewhat lower than the rates in European and French-Canadian population (Table 4).

14. Folypolyglutamate Hydrolase (GGH)

GGH is a lysosomal peptidase that catalyses the removal of gamma-linked polyglutamates and convert long-chain polyglutamates (n=4–7) into short-chain polyglutamates (n=2–3) and ultimately MTX, allowing folate to be exported from the cell [94].

Several SNPs have been identified in the GGH gene at bases -401C>T, -354G>T, -124T>G, +16T>C, +452C>T, and +1102A>G; these sites comprise both the promoter and the coding region [95, 96]. Nevertheless, few SNPs have been associated with catalytic activity of the GGH in B- and T-lineage ALL cells, and greater accumulation of long-chain MTX in these cells [97].

The polymorphism +452C>T in the transcribed region of GGH gene alters Thr-127 to Ile-127I, and has been associated with reduced catalytic activity in hyperdiploid B- and T-lineage acute lymphocytic leukemia (ALL) cells, and greater accumulation of long-chain MTXPG in these cells [97]. In contrast, all of the promoter polymorphisms enhanced GGH expression and an increased GGH activity may lead to decreased accumulation of MTXPG and to MTX resistance. At least one of these, -401C>T, has been shown to be correlated with decreased accumulation of long-chain MTX-Glu3–5 in rheumatoid arthritis patients treated with MTX [98].

Only polymorphism -354G>T has been associated with survival of children with ALL. -354GT or -354TT genotypes carrier have better probability of 5-year post-treatment OS compared to -354GG genotypes ($p = 0.04$) (Table 4) [99]. This shows the enzyme GGH clearly plays an important role in the metabolism of folates and anti-folates. However, unambiguous demonstration of a direct role of GGH in anti-folate drug resistance has been difficult. Part of the difficulty is that GGH is only one of several factors that can affect anti-folate levels, and its role presumably is directly linked to those of the other enzymes. [100]. However, these studies have demonstrated that polymorphisms in GGH increase promoter activity and an increased GGH activity may lead to decreased accumulation of MTXPG and to MTX resistance [101]

Genotypes	Population	Survival estimated	% of Overall Survival	Number of patients	Ref.
80A>G polymorphism in RFC1 gene					
G/G	Italian (adults)	At 5 years	59.0	13	[102]
A/G + A/A			28.0	34	
G/G	Mexican (children)	At 5 years	76.0	20	[103]
A/G + A/A			42.0	50	
G/G	European (children)	At 5 years	97.0	160	[104]
A/G + A/A			75.0	305	
G/G	French-Canadian origin (children)	At 5 years	89.0	61	[93]
A/G + A/A			76.0	143	
-354G>T polymorphism in GGH gene					
GG	European (children)	At 5 years	90.0	123	[99]
GT+TT			>90.0	116	
-317A>G polymorphism in DHFR gene					
A/A	Mexican (children)	At 5 years	78.0	14	[105]
A/G + G/G			41.0	56	
A/A	Canadian (children)	At 5 years	92.0	24	[106]
A/G + G/G			76.0	31	
829C>T polymorphism in DHFR gene					
C/C	Mexican (children)	At 5 years	80.0	10	[105]
C/T + T/T			38.0	60	
Polymorphism in TS gene					
3R/3R-negative	Canadian (children)	At 5 years	82.0	193	[107]
3R/3R-positive			71.0	66	
2R/2R or 2R/3R	French-Canadian (children)	At 5 years	87.0	155	[108]
3R/3R			68.0	50	
677C>T polymorphism in MTHFR gene					
C	Italian (Adults)	At 2 years	55.0	118	[109]
TT			14.0		
C	Spanish (children)	At 4 years	98.0	106	[110]
TT			52.0	35	
C	Egyptian (children)	At 2 years	90.9	22	[111]
TT			50.0	4	
T677A1298 haplotype of the MTHFR gene					
T677A1298 (-)	French–Canadian origin (Children)	At 5 years	89.0	84	[112]
T677A1298 (+)			74.0	117	

Table 4. Genetic polymorphism and its relationship to survival in ALL

15. Dihydrofolate Reductase (DHFR)

DHFR is responsible to catalyze the reduction of dihydrofolate (DHF) to tetrahydrofolate (THF) [113]. The major mechanism of MTX action involves competitive inhibition of DHFR, leading to the impaired regeneration of THF from DHF; essential for the biosynthesis of purines and thymidylate, thus it also blocks the *de novo* synthesis of DNA [114, 115].

Changes in the levels of DHFR expression and consequently in the sensitivity to MTX can also be due to single SNPs, particularly those located in the regulatory elements [105]. The C829T SNP is located at the 223 nucleotide downstream from the stop codon between the first and second polyadenylation sites in the 3'UTR of the DHFR gene, which leads to the stability of mRNA [116]. A previous study reported that the -A317G SNP in the DHFR promoter region results in higher transcriptional activity [106]. Recently demonstrated an association between G/G and T/T genotypes of the -A317G and C829T polymorphisms and reduced survival in pediatric patients with ALL (Table 4).

16. Thymidylate Synthase (TS)

The TS is a key enzyme in the nucleotide biosynthesis and important target of several chemotherapeutics. TS provides the only source for *de novo* thymidylate production by catalyzing the methylation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) [107]. TS is efficiently inhibited by the uracil analog, 5-fluorouracil (5-FU) and MTX, used for many years as a treatment for a variety of cancers.

The most common polymorphism in TS is a unique double (2R) or triple (3R) 28-bp tandem repeat sequence in the 5' untranslated region (5'-UTR) of the TS gene also called TS enhancer region (TSER), immediately upstream from the initiation site, which influences protein expression in cancer cells [117]. The presence of a triple versus double 28-bp repeat in the enhancer region has been associated with an increased TS expression both in *in vivo* and *in vitro* studies [118, 119].

Previous studies have shown that pediatric patients who were homozygous for the triple repeat (3R/3R) had a poorer prognostic (odds ratio 4.1, 95% CI 1.9–9.0, $p=0.001$) [108] and shorter survival than those patients with other genotypes (Table 4).

17. Methylenetetrahydrofolate Reductase (MTHFR)

The MTHFR is a key folate enzyme that catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate in the folic acid cycle, and is interrupted by methotrexate (MTX), a critical chemotherapy agent in ALL therapy [120].

Despite the fact that several MTHFR polymorphisms have been described thus far, only two polymorphisms, C677T and A1298C, have been intensively investigated. The C-to-T transi-

tion at the nucleotide position 677 in exon 4 of MTHFR generates an alanine-to-valine substitution at amino acid 222 [121]. As a result, carriers of the MTHFR 677TT genotype possess a thermolabile enzyme of reduced activity [122]. The second most studied polymorphism in MTHFR is an A-to-C transversion substitution at nucleotide 1,298 (exon 7) that results in an amino acid substitution of glutamate for alanine at codon 429 [123]. Once this amino acid substitution takes place at the S-adenosylmethionine regulatory domain of the MTHFR, the A1298C polymorphism also generates an enzyme with a decreased activity [123]. Other investigators have reported that A1298C and C677T polymorphisms in MTHFR gene are associated with disease outcomes and survival both in children and adults (table 4).

The overall survival rate of MTHFR 677TT and 1298CC carriers was lower than that of patients carrying MTHFR C or A alleles respectively. A limited amount of evidence has been reported on the influence of MTHFR polymorphisms on survival.

18. Methylenetetrahydrofolate Dehydrogenase (MTHFD1)

MTHFD1 is an enzyme involved in folate metabolism, which plays an important role in the generation of the 5,10-methylene-THF and 10-formyl-THF. The last two are the donor cofactors for de novo purine and pyrimidine biosynthesis and, thus, for the biosynthesis of DNA [124]. The G to A substitution at position 1958 of the MTHFD1 gene, causing an alanine to glycine substitution at codon 653 located within the 10-formyl-THF synthetase enzyme domain, which reduces the enzyme's activity [124].

A analysis of 201 children treated with methotrexate showed that patients with the MTHFD1 A1958 variant had a remarkably lower probability of 5-year post-treatment survival, compared to subjects with no event-predisposing genotypes (45.0% vs 95.0%, p=0.0002) [112].

Expression	Population	Survival estimated	% of Overall Survival	Number of patients	Ref.
Negative	Korean (Children and Adults	At 2 years	>85.0	24	[125]
Positive			<55.0	8	
Low	Brazilian (Childen)	At 5 years	81.0	150	[126]
High			54.0		
Low	European (Children)	At 5 years	87.2	56	[127]
High			60.0		
Low	European (Adults)	At 5 years	80.0	49	[127]
High			52.0		

Table 5. Expression of MRP1 and its relationship to survival in ALL

19. Multidrug Resistance-Associated Protein 1 (MRP1/ABCC1)

Multidrug resistance (MDR) is one of the major obstacles in cancer chemotherapy. Over-expression of ATP-binding cassette (ABC) transporters, such as P-glycoprotein (Pgp/MDR1/ABCB1) and multidrug resistance-associated protein 1 (MRP1/ABCC1), have been shown to cause MDR in model cell lines and in clinical settings [128-130]. Currently, eight MRP genes have been identified, of which the MRP transporters (MRP1-6) are known to be involved in extruding substrates that are generally used in the treatment of ALL, including doxorubicin, vincristine, etoposide, 6-mercaptopurine, and methotrexate [131-134].

Recent studies have shown that in ALL patients, high expression of MRP1, is a highly significant indicator of poor response to chemotherapy and poor overall survival in both in children and adults (Table 5).

20. Summary and future directions

Several clinical and biological features have been associated with the improved survival of patients with ALL, including age, sex, WBC, race/ethnicity, immunophenotype, recurrent chromosomal abnormalities, and genetics polymorphisms. The application of risk-stratified therapy utilizing these prognostic factors has resulted in long-term event-free survival in up to 80-85% of patients with ALL. Further improvement in outcome will require, in part, the discovery of novel prognostic factors, (such as, genetic variation in the folate pathway, transport of drugs, as well as miRNAs expression) to identify the 15-20% of patients who are not cured with current therapies. Recent advances in our understanding of underlying leukemia biology, including the identification of prognostically distinctive subsets of patients, and of host pharmacogenomics may allow for more precise risk stratification and more targeted, individualized treatment planning that will lead to higher survival of the patients with ALL.

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