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Chapter

Acute Lymphoblastic Leukemia in Adolescents and Young Adults

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Abstract

When diagnosed with ALL the age group between 18 and 45 years old (AYA, adolescents and young adults) do not have the good prognosis factors generally observed in children with this diagnosis. For a long time, it was undetermined whether they should be treated with continuous and sustained chemotherapy as children or whether receive sustained chemotherapy, but with longer rest periods like old adults. The medical care of adolescents and young adults with neoplastic diseases, grouped between 15 and 45 years of age, became an emerging research field of treatment in hematological diseases. Outcomes have asses complete response disease-free survival, and overall survival as markers of response, with very poor results reported. Relevant challenges have been identified in the AYA group with ALL that have drawn attention to the need to increase research in this area, particularly in the care of the population under 45 years of age with hematological malignancies.

Keywords: acute lymphoblastic leukemia, remission, relapse, treatment, adult young and adolescents, bone marrow transplant

1. Introduction

Acute lymphoblastic leukemia (ALL) is an oncohematological disease caused by genetic changes that alter the differentiation and proliferation of lymphocytes, distinguished by the infiltration of bone marrow, blood, and other tissues by neoplastic cells of hematopoietic origin [1]. The pathophysiology of these disease include causes for which, certain genes result affected in their function. Patients could present the following symptomatology: fever, lymphadenopathy, coagulation disorders, anemia, hepato-splenomegaly, weight loss, among others.

Another definition of ALL could be a disease caused by an acquired or congenital injury to the hematopoietic cell DNA (the genetic material) developing in the bone marrow, once these cells transform into a leukemic clone multiplies uncontrollably and rapidly in billions of malignant cells called lymphoblasts that prevents the

normal cellular production of leukocytes, platelets and red blood cells. As a result, when a patient is diagnosed with acute lymphoblastic leukemia, the number of healthy blood cells (red blood cells, white blood cells, and platelets) could be less than normal, although it is not uncommon to see an exaggerated elevation of white blood cells but all of them lymphoblasts.

It is more frequent in childhood than in adulthood, being the most common type of leukemia in children, with a peak of incidence between the 2 and 4 years old. When it appears in adulthood, it implies a worse prognosis.

2. Diagnosis by flow cytometry

There are a group of important cellular markers to make the diagnosis of B cell lineage, those are: CD19, CD20, CD22, CD24, and CD79a. The principal and earlier markers for lineage B cells are CD19, CD22 (membrane and cytoplasm respective) and CD79a [1, 2]. The presence of either of these two markers, without further differentiation markers, identifies the neoplastic cell as pro-B ALL (EGIL BI subtype). Positivity of the CD10 antigen (CALLA) defines the neoplastic cell as "common ALL" (EGIL B-II subtype). Cases with additional identification of the cytoplasmic heavy Mu chain are classified as the pre-B group (EGIL B-III subtype), while the presence of surface immunoglobulin light chains as mature B-ALL (EGIL B-IV subtype) [3].

In recent years, the direct correlation between ontogenetic classification with immunophenotypic expression by flow cytometry and cytogenetic or molecular alterations in type B acute lymphoblastic leukemia has been described (**Table 1**) [3–6].

T-cell ALL constitutes 25% of adult ALL cases. Characteristic T cell markers are CD1a, CD2, CD3 (membrane and cytoplasm), CD4, CD5, CD7, and CD8. CD2, CD5 and CD7 antigens are markers of immature T cells, but none of them is absolutely lineage-specific, so the unequivocal diagnosis of T-ALL is based on the demonstration of superficial / cytoplasmic CD3. In T-ALL CD10 expression is quite common (25%) but non-specific, CD34 andCD13 and / or CD33 myeloid antigens can also be expressed by these cells. The recognized T-ALL subgroups: pro-T EGIL TI (cCD3 +, CD7 +), pre-T EGIL T-II (cCD3 +, CD7 + and CD5 / CD2 +), cortical T EGIL T-III (cCD3 +, Cd1a +, sCD3 + / -) and mature-T EGIL T-IV (cCD3 +, sCD3 +, CD1a−) [3–7].

PRECURSORS	ONTOGENICS	INMUNOPHENOTYPE	MOLECULAR CYTOGENETIC
	Pro B	CD 10(-), CD 34 (++), CD 20(-), TdT(++)	t(v;11q23.3), rearrangement MLL (KMT2A), t(4;11)
CD 19 (+), CD 22 (+), CD79a(+), HLA-DR(+)	Common	CD10 (+++), CD 34(+), CD20 (-/+), Cadena μ (-), TdT (++)	t(9;22) (q34.1;q11.2)(BCR-ABL1), t(12;21)(p13.2;q22.1) (TEL-AML1/ ETV6-RUNX1); t(5;14)(q31.1;q32.3) (IL3-IGH); hiperdyploid, hipodyploid
	Pre B	CD 10(+), CD34(-), CD20(+), Cadena μ (+), TdT ++	t(5;14)(q31.1;q32.3) (IL3-IGH); hiperdyploid, hipodyploid
	Mature	CD20(+), TdT(-), CD10 (+), CD34(-), k(+) o λ(+)	rearregment of MYC, t(8;14), t(2;8), t(8;22)

Table 1.
Immunogenetic classification of B ALL.

PRECURSOR	ONTOGENICS	INMUNOPHENOTYPE	MOLECULAR/ CYTOGENETIC
	Pro T (T I)	CD2(-), CD5(-), CD8(-), CD4 (-), TdT(++), CD34(+/-)	*NOTCH 1 t (10;14) HIX 11-TCR* t (11;14) LMO/TCR NUP213 ABL1 HOX11
CD7(++), (CD3c(+), CD3m(-/+) débil	Early T	CD5(+) d,CD8(-), CD1a(-), CD2(-), TdT(+)	
	Pre T (T II)	CD2(+) y/o CD5(+) y/o CD8 (+), CD1a(-), mCD3(-)	
	Intermedia or cortical T (T III)	CD1a(+),CD34(-), CD4(+), CD8(+), CD3m(+)	
CD7(++), CD3c(+), CD3m(+)	Mature T	CD3m(+), CD1a(-), TCRαβ(+) o TCRγδ(+)	———————

Table 2.
Immunogenetic classification of T cell.

The ontogenetic and immunocytogenetic correlation have particular importance due to prognostic relevance in both B-cell and T-cell lymphoid leukemia. **Table 2** shows the correlation between the different T cell-type leukemia.

3. Cytogenetic diagnosis

The karyotype alterations that could be found in ALL are numerical and structural changes as well, that have profound prognostic significance. Cytogenetics analysis represents an important step in ALL classification. The conventional karyotype can be useful in identifying recurring translocations, as well as in the identification of gain or loss of chromosomal material; However, the biggest limitation of this technique is the requirement of the cell to enter in metaphase, what is necessary for the obtaining of the material for the analysis of chromosomes. In such cases the technique of fluorescence in situ hybridization (FISH) can allow direct detection and visualization of virtually all investigated chromosomal abnormalities in ALL, with a sensitivity near of 99%, finally, comparative genomic hybridization of matrices (matrix-CGH, a-CGH) and matrices of single nucleotide polymorphisms(SNPs) can allow the identification of cryptic and/or submicroscopic changes in the genome [8, 9].

3.1 Cytogenetic/genetic risk groups

The aberrations with a good prognosis are: del(12p), t(12p) / t(12; 21) (p13; q22) t(10; 14) (q24; q11) in ALL of lineage B. These abnormalities are relatively rare in adults compared to childhood with ALL.

Aberrations associated with intermediate risk include the normal diploid subset plus cases of hyperdiploidy and various other recurrent or random chromosomal abnormalities.

Other aberrations such as isolated trisomy 21, trisomy 8, and perhaps del(6q) and t(1; 19) (q23;p13) / E2A-PBX1 may constitute an intermediate-high risk group; Recent evidence suggests that the previously poor prognosis reported for t (1, 19) (q23; p13) / E2A-PBX1 could be outweighed by some current therapeutic approaches [10, 11]. Other newly identified aberrations in the intermediate-high risk group are iAMP21 12 and IGH rearrangements, including CRLF2 [12, 13].

Finally, patients with t(9; 22) (q34; q11) or BCR-ABL1 rearrangement with positive FISH test (Philadelphia + ALL), t (4; 11) (q21; q23) or MLL rearrangements

at 11q23, monosomy 7, hypodiploidy (and the closely related near triploid group) fell into the high-risk cytogenetic category, with a disease-free survival (DFS) rate of approximately 25%, or 10% in the specific case of Phi + ALL prior to introduction of tyrosine kinase inhibitors (TKI) [14, 15]. The presence of the Phi + chromosome in ALL can constitute 25–50% of CD10 + or pre-B cases and represent the most frequent alteration in adult and elderly patients, found in more than 50% of cases in the 6th decade of life [16]. Secondary chromosomal abnormalities in addition to t(9; 22) (q34; q11) may worsen the prognosis [17] however this has not yet been proven in the TKI era [18]. Currently the most group with the most unfavorable prognosis among cases with known genetic / molecular aberration is represented by t(4; 11) (q21; q23) with MLL1 rearrangement unless an allogeneic hematopoietic stem cell transplantation is performed [19].

Some other karyotypes alterations are exclusive to specific ALL syndromes. Translocations involving chromosome 8 (MYC gene), as well as t (8; 14) (q24; q32) (90% of cases), t (8; 22) (q24; q11) (10% of cases) and t (2;8) (rarely observed) are practically present in 100% of cases of mature B-ALL with L3 / Burkitt morphology and immunoglobulins in the clonal surface. Typical cytogenetic aberrations are also found in the T lineage, the most frequent involve resection points of 14q11, for example, t (10; 14) (q24; q11), t (11; 14) (p13; q11) and others, the presence of t (8; 14) with resection points at q24; q11 (q24; q32 in line B ALL) in T cell ALL is associated with aggressive lymphomatous presentation [20–22].

An interruption in IKZF1 encoding the Ikaros transcription factor has been frequently observed in ALL with BCR / ABL rearrangement (80% of cases). The IKZF1 mutation predicts poor outcome in the treatment of ALL, Phi+ or not [13, 23–25].

By integrating genome-wide technologies the "BCR / ABL-like" subgroup has been suggested and identified in adult and child populations [26, 27] and represents approximately 15% of ALL ontogeny B cases. This subgroup It is characterized by a gene expression that is similar to that of BCR/ABL + patients, with frequent detection of the IKZF1 mutation and CRLF2 rearrangements but with where abysmal differences in the outcomes. Other mutations and / or rearrangements that activate tyrosine kinases has also been revealed as poor prognosis factor such as rearrangement of IGH-CRLF2, NUP214-ABL1, EBD1-PDGRB, BCR-JAK2 fusions and STRN3 JAK2, which have been associated with a very poor prognosis [28].

Hypodiploid ALL, considered a high risk factor has been extensively evaluated in pediatric ALL [29] Alterations involving tyrosine kinase receptors and RAS gene signaling (i.e., NRAS, KRAS, FLT3, and NF1) can be detected in up to 70% of haploid cases, while hypodiploid cases are characterized by lesions involving members of the Ikaros family, particularly IKZF2 and by TP53 interruptions which can be identified in 91.2% of these. In adult ALL, these cases are characterized by non-random chromosome loss and CDKN2A / B with locus deletion as the only recurrent abnormality; As previously reported, in children these cases often harbor TP53 mutations [30].

The TP53 mutation is detected in 6.4% of all ALL cases and a correlation with a worse result has been demonstrated. In adults, TP53 mutations are identified at diagnosis in 8.2% of cases (11.1% of T-ALL and 6.4% of B-ALL), and are preferably identified without molecular aberrations and are associated with refractoriness to chemotherapy [31, 32].

In T cell-ALL, well-recognized aberrations are: Rearrangement of the T-cell receptor (TCR) gene, chromosomal deletions and focal gene deletions, in addition, chromosomal rearrangements can also lead to fusion genes in the framework of Chimeric proteins with oncogenic properties such as thePICALM-MLLT10, NUP214-ABL1 fusion for medin episomes, EML-ABL1, theSET-NUP214 fusion and MLL-type genetic rearrangements have uncertain significance [33, 34].

Cytogenetic alterations	Gene	Frequency in adults	Frequency in children
Hypodiploidy (>50 chromosomes)	–	7%	25%
Hypodiploidy (<44 chromosomes)	–	2%	15
t(9;22) (q34;q11):Philadelphia chromosome(Ph+)	BCR-ABL1	25%	2-4%
t(12,21) (p13;q22)	ETV6-RUNX1 (TEL-AML1)	2%	22%
t(v;11q23), t(4;11), t(11;19)	KMT2A	10%	8%
t(1;19) (q23;p13)	TCF3-PBX1 (E2A-PBX1)	3%	6%
t(5;14) (q31;q32)	IL3-IGH	< 15	<1%
t(8;14), t(2;8), t(8;22)	c-MYC	4%	2%
t(1;14)	TAL-1	12%	7%
t(10;14) (q24;q11)	HOX11 (TLX1)	8%	15
t(5;14) (q35;q32)	HOX11L2	1%	35
t(11;14) (q11)(p13;q11) (p15;q11)	TCR y TCR	20-25%	10-20%
BCR-abl1-like/Ph-like	Multiple	10-30%	15%
LLA-B con iAMP21	RUNX11	–	2%
ETP	Multiple	2%	25%
Ikaros	IKZF1	25-35%	12-17%

Table 3.
Frequency of Chromosomic and molecular alterations by age group.

A large set of mutations in T cell-line ALL has been identified by sequencing techniques including NOTCH1, FBW7, BCL11B, JAK1, PTPN2, IL7R and PHF6, some of them have recognized prognostic importance, while others require further investigation. In fact, NOTCH1 and / or FBW7 mutations that occur in more than 60% and around 20% of cases, respectively, are generally associated with a favorable outcome. A new prognostic model has been recently proposed defining as low risk those with NOTCH1 and FBW7 mutations and those with lesions involving RAS/PTEN as high-risk. JAK1 mutations, which increase JAK activity and impair

Risk	Cytogenetic alterations
Good	• Hypodiploidy (51-65 chromosomes) • Cases with trisomy 4,10 y 17 more favorable results • t(12;21) (p13;q22):ETV6-EUNX1[a]
Poor	• Hypodiploidy • KMT2A, t(4;11) • t(v;14q32)/IgH • t(8;22)(q34;q11.2):BCR-ABL1 • Complex karyotype (5 o more abnormalities) • Ph-like ALL intrachromosomal amplification 21(iAMP21)

Table 4.
Cytogenetic risk groups.

B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);BCR-ABL1
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);KMT2A rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1);ETV6-RUNX1
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) IL3-IGH
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);TCF3-PBX1
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma
Modified of D´Angelo, 2006 [37].

Table 5.
WHO classification of lymphoblastic leukemia.

proliferation and survival, have been associated with refractoriness of chemotherapy and should be considered as poor prognosis markers [35, 36].

Recurrent chromosomal and molecular abnormalities characterize ALL subtypes in adults and children (**Table 3**) and often provide prognostic information that can influence risk stratification and treatment decisions (**Table 4**). The frequency of certain subtypes differs between adult and child ALL, what partially explains the difference in clinical outcomes between patient populations [6, 30, 34, 36].

The most recent classification of the World Health Organization (WHO) for acute lymphoblastic leukemia ins shown in **Table 5**.

4. Treatment

The evolution in treatment of patients with ALL has progressed over time, this in order to achieve better survival, relapse-free rates and the quest to achieve cure. We will divide this issue into two large groups: AYA group (adolescents and young adults) and the group of people over 40 years old; and subdivided focusing on status of Philadelphia chromosome (positive and negative).

Chemotherapy treatment is divided into treatment phases with different goals: [38, 39].

Induction: it is the phase that seeks to achieve remission normalizing the parameters of the blood count (Hb >10 gr/dl, Neutrophils >1000 /mm3, platelets >100,000/mm3) as well normalization of the organs affected by diagnosis (liver, kidney, lung).

Consolidation: in this phase, the aim is to keep the patient in remission and achieve a negative minimal residual disease (MRD) that will impact the prognosis.

Maintenance: this phase seeks to avoid relapse of the disease and prepare for an elective suspension [38–40].

5. Treatment of the AYA group

This group is considered as a "superimposed" population since pediatric schemes have improved their degrees of response compared to adult designed schemes. Initially, the treatment regimens in this group of patients were based on regimens for adults, showing complete remissions in a low percentage, a couple of examples are the UKALLXII/ECOG [41] case study that reported complete remission (CR) nearly 51% after 1 chemotherapy cycle with increase to 91% after 2 induction cycles and the CALGB8811 [42] study that reported RC of 62–86% after 1 and 2 cycles of induction to remission respectively; On the other hand, the LALA-94 [43] study reported CR rate of 72% after one treatment cycle up to 84% after 2 treatment cycles, thus we have to mention the Hyper-CVAD scheme with a CR rate in the first cycle reported in 81% with increase after 2 cycles to 92% [44]; the DFCI45 pilot study showed an RC of 82% in the first induction cycle. Due to the above, it's clear that treatment schemes based on adults' schemes are ineffective to achieve CR, for these reasons the AYA Group was separated looking for different treatment schemes which includes two large groups, those based on pediatric schemes with expansion in the group of age and modified pediatric inspiration schemes (**Tables 6** and 7).

By reviewing the pediatric regimens with extension to the age group of treatment was possible to increase the degree of response in this group classified as AYA; in adult regimens, complete remissions ranging from 51% to a maximum of 82% were reported after 1 cycle of treatment, however, in **Table 1** we observe that pediatric regimens in general achieved a higher percentage of complete response or remission after applying 1 cycle of induction, showing with the highest degree of complete response in 98% of the cases for the studies: TOTAL TERAPY IV, 46 PETHEMA ALL 96.47 DCOG, 58 ALL97.59, however, it should be noted that the study with greater robustness in this group that showed the highest CR is the

Studies	Number of cases	Age (rank)	% CR	DFS (years/%)	OS (years/%)	Ref.
CCG 1961	262	16-21	95	5/72	5/78	[38]
DFCI9101/9501	51	15-18	94	5/78	5/81	[40]
UKALL 2003	229	16-24	97	5/72	5/76	[39]
TOTAL TERAPY XV	45	15-81	98	5/86	5/88	[45]
PETHEMA ALL 96	81	15-30	98	6/61	6/69	[46]
HOVON (FRALLE 93)	54	17-40	91	2/66	2/72	[47]
NOPHO 2008	221	18-45	NR	5/74	5/78	[48]
FRALL 2000	186	15-19	96	5/74	5/80	[49]
INTERGROUPC10403	296	17-39	NR	2/66	2/79	[50]
FRALLE93	77	15-20	94	5/67	NR	[51]
DCOG	47	15-18	98	5/69	5/79	[52]
ALL97	61	15-17	98	5/65	NR	[53]
AIEOP	150	14-18	94	5/67	5/67	[54]

CR: Complete Remission, Ref. Reference, DFS: Disease Free Survival, OS: Overall Survival, NR: Not Reported.

Table 6.
No comparative studies of pediatric regimens.

Studies	Number of cases	Age (rank)	% CR	DFS (years/%)	OS (years/%)	Ref.
DFCI 01-175	74	18-50	86	4/58	4/67	[55]
MODIFIED DFCI 91-01	42	18-35	98	3/77	3/83	[56]
GRAALL2003/2005	502	15-35	95	5/59	5/65	[57]
GMALL 07/03	887	15-35	91	5/61	5/65	[58]
MODIFIED TPOG	35	15-39	89	2/47	2/50	[59]
LALIN	20	15-25	90	5/70	NR	[60]
NOPHO-92	144	10-14	99	5/65	NR	[61]

CR: Complete Remission, Ref. Reference, DFS: Disease Free Survival, OS: Overall Survival, NR: Not Reported.

Table 7.
Pediatric inspired schemes.

Studies	Number of cases	Age (rank)	% CR	DFS (years/%)	OS (years/%)	Ref.
Hyper-CVAD	185	>60	91	5/39%	5/10	[62]
SMOG 8419	85	50-84	41	5/32	5/<10	[63]
GIMEMA 0288	778	12-59	82	2/50	9/27	[64]
CALGB	280 350 129	<30 30-59 >60	90 81 57	3/47 3/38 3/18	3/58 3/38 3/18	[65]
PETHEMA ALL96	33	56-67	58	2/39	2/46	[66]
MRC UKALLXII/ECOG2993	100	55-64	70	5/19	5/21	[67]
GMALL	268	55-85	76	NR	5/23	[68]
HOSPITAL EDOUARD HERRIOT, LYON	195 118 66	<35 35-60 >60	84 85 58	3/35 3/31 3/11	3/39 3/34 3/11	[69]
MD ANDERSON, HOUSTON	65 64 31 44	<30 30-49 50-59 >60	98 89 93 79	3/53 3/55 3/34 3/36	5/54 5/42 5/29 5/17	[70]
ALL-07FRAIL	72	57-89	54	6.9 month	7.6 month	[71]

CR: Complete Remission, Ref. Reference, DFS: Disease Free Survival, OS: Overall Survival, NR: Not Reported.

Table 8.
Treatment schemes for ALL in adults.

PETHEMA ALL 96.47 study, which shows a reported follow-up at 5 years with evidence of DFS of 61% OS of 69% at 6 years. On the other hand, it is important to mention that the Intergroup C1040351 study observed a 2-year DFS of 66% and an OS of 79%. In all the groups referred to in **Table 8**, the degree of CR registered was greater than 90%, but with different DFS and OS times, the longest DFS time for the DCOG study, which was 69% at 5 years and OS of 79% at 5 years.

Of the pediatric inspiration schemes, we refer to those registered in **Table 9**, all of them report CR greater than 90%, with the exception of studies DFCI01–17552 and MODIFIED TPOG 56 where the lowest degree of CR of 86 and 89%,

Studies	Number of cases	Age (rank)	% CR	DFS (years/%)	OS (years/%)	Ref.
GMALL (Imatinib)	28	54-79	96	2/19	2/42	[72]
PETHEMA ALL0PH07 (Imatinib)	53	56-88	87	38months	37.3 months	[73]
HyperCVAD + Imatinib	54	17-84	93	5/43	5/35	[74]
GIMEMA LAL0201-B (Imatinib)	29	61-83	100	1/48	1/74	[75]
EWAL-PH-01 (Dasatinib)	71	59-83	96	5/27	5/36	[76]
GIMEMA LAL1205 (Dasatinib)	53	18-77	100	2/51	2/69	[77]
HyperCVAD plus Dasatinib.	72	21-80	96	5/42	5/52	[78]
EWALL-PH-02 Nilotinib	65	55-85	87	NR	NR	[79]
Korean study Nilotinib	90	17-77	91	2/72	2/72	[80]
HyperCVAD + Ponatinib	37	27-55	100	2/81	2/80	[81]
GIMEMA + Ponatinib	42	27-85	91	3/69	3/83	[82]

CR: Complete Remission, Ref. Reference, DFS: Disease Free Survival, OS: Overall Survival, NR: Not Reported.

Table 9.
ALL Phi positive treatment.

respectively, is recorded. Likewise, the DFS reported in the MODIFIED TPOG group is lower, being 47% of the cases at 2 years. In this same table we observe the two studies with the largest number of patients, the GRAALL2003 / 200,554 study with a number of subjects analyzed of 502 cases and for the GAMALL55 study 887 cases, with a similarity in the DFS reported for the GRAALL2003 / 2005 of 59% at 5 years and for GMALL07 / 03 from 61% at 5 years and similar OS in both groups from 65% at 5 years; the aforementioned has generated improvement in responses and survival in the AYA groups, so the current recommendations are aimed at treating pediatric schemes or modified schemes of pediatric-inspired protocols.

Those patients over 40 years old are considered as "adults" an represent totally different group when comparing with the pediatric and AYA groups when talking about prognosis and treatment. The age by itself is a conditioning factor for a lower response rate, lower DFS, and poorer OS compared to the AYA group, this data is summarized in **Table 8**. This group have hematological remission variable and those with lesser degree of Response rate are adults over 65 years, with a percentage of CR ranging from 41 to 60% according to the ALL-07FRAIL72 studies and the SMOG 841964 study. As illustrated in **Table 3**, in the Edouard Herriot Lyon Hospital, the population of 35–60 years old reached a CR of 85% but this was lower in the group over 60 years with CR reported in 58% [69]; as well as the study of the MD Anderson with the HyperCVAD [62] scheme where the age groups of 30 to 49 years, 50 to 59 years and over 60 years reached a CR of 98%, 83%, 79% respectively [70]. In the same way, the DFS and OS for the Hyper CVAD group of the GIMEMA study 028865 was lower in the older groups, 39% at 5 years and an OS with a longer duration of 27% at 9, in general we conclude that the older age could be related to lower rate of CR, DFS and OS.

All those previously described have been mainly in the groups cataloged as Phi negative ALL, as they are not carriers of the BCR / ABL oncogene, however, in the group that is a carrier of these genetic alteration treatment will be describe in

Table 9, where the different percentages of response between these and those Phi negatives are observed.

In the GMALL73 study the benefit of adding a tyrosine kinase inhibitor (TKI) to non-intensive regimens in elderly patients was initially observed. In this study a group was randomized to receive chemotherapy (CT) + TKI vs. CT, and was observed that adding an TKI achieved a CR of 96%, the double from the RC of 50% seeing in patients who were not treated with imatinib. In this patient group it is striking that adding TKI to a conventional chemotherapy scheme offers the benefit of even higher CR than those presented in populations older than 40 years, as reported in the studies of the Italian group (GIMEMA, LAL0201-B and GIMEMA LAL1205) [75, 77]with CR of 100% with 1st and 2nd generation inhibitor of TKI, however, the DFS and OS were brief in both groups, being higher in the group that received dasatinib (2nd generation TKI) as induction therapy and with a younger population that predicts the higher degree of response. It is worth mentioning that the second-generation TKI dasatinib has Central Nervous System (CNS) penetration showing improved response and survival of cases with CNS infiltration compared to imatinib that fails to cross the blood–brain barrier. **Table 4** records the treatment given by the MD Anderson group, which showed that adding a 3rd generation TKI as ponatinib to the HyperCVAD scheme achieved 100% CR in the group aged 27 to 55 with DFS and OS at 2 years of 81 and 80% respectively [81]. It should be mentioned that ponatinib has good CNS penetration as does dasatinib, however ponatinib is indicated in patients with the T315I resistance mutation.

A meta-analysis of 15 studies with a total of 11,040 patients with ALL Phi positive shown that the highest prevalence of Phi positive is seeing in those between 11 and 40 years old (25.8% to 26.2%.) By age subgroup the reported prevalence was: 1–10 years 15.6%, 10–20 years 25.6%, 21–40 years of age 26.2% and in the group over 40 years of age 16.9%. In this meta-analysis, the overall 5-year survival rate was 42.8% (CI 95% CI, 23.9–64.1, I2 93) [83].

6. Prophylaxis to CNS

Intrathecal chemotherapy is pivotal in the treatment of ALL since the CNS is a site of relevance in this pathology. In adult ALL involvement of the CNS at diagnosis is reported in 5–7% of cases, mainly with meningeal involvement. The risk factors related to initial infiltration are elevated Lactic Dehydrogenase (LDH), hyperleukocytosis and ALL B subtype at diagnosis, the latter showing CNS involvement in up to 18% of cases. Other factors that contribute to the initial infiltration are increased blast replication rate, mediastinal mass, and positive Phi [84]. These same factors contribute to the early relapse of the disease, systemically or in isolation to the CNS. For the diagnosis of infiltration, the microscopic examination of cerebrospinal fluid (CSF) obtained from a lumbar puncture continues to be the standard and classified the cases into risk groups according to the number of leukocytes, and the presence of blasts (**Table 10**) and the nature of the lumbar puncture, as well as determination by flow cytometry.

Traumatic Lumbar puncture (TLP) is defined as a result of CSF with erythrocyte count>10 /uL. The Stevenherz/Bleyer algorithm evaluates traumatic puncture if the patient has leukemic cells in peripheral blood and the lumbar puncture is traumatic and contains >5 leukocytes/uL and blasts, the following algorithm should be followed to distinguish between CNS2 disease and CNS3: CSF leukocytes/erythrocytes >2 x leukocytes in blood/red blood cells [84, 85].

Effective prophylaxis to prevent CNS relapse is an essential part of ALL regimens, the most used modalities are based on CNS irradiation, intrathecal

Classification	Lymphoblasts in CSF	Leucocytes in CSF
SNC 1	None	
SNC 2	Present	<5
SNC 3	Present	≥5
TLP	Present	Variable

CSF, cerebrospinal fluid; CNS, central nervous system; traumatic lumbar puncture (TLP).

Table 10.
Classification of the CNS infiltration according to the CSF characteristics.

chemotherapy with a single drug or with steroid-based triplet plus cytarabine and methotrexate at same time as systemic CT is being administrated. With these measures the relapse rate can be reduced from 10 to 5%. Irradiation as a single dose of 24 Gy is recommended as unique therapy to the skull without involving the neuroaxis to avoid cytopenia associated with concurrent CT [86]. In cases of ALL Phi +, although dasatinib and ponatinib are not part of prophylaxis therapy these have been shown to cross the blood–brain barrier and secondarily reduced the risk of isolated relapse to the CNS [87, 88].

7. Hematopoietic stem cell transplant

Hematopoietic stem cell transplant (HSCT) in patients with Acute Lymphoblastic Leukemia is a therapeutic option in those with high risk disease that have reached complete response (CR) and those who are candidates by the Predictive Models of Risk (Disease Risk Index (DRI), EBMT Risk Score, HCT-Comorbidity Index). the patients could be classified in 3 different risk groups (0 points = low risk, 1–2 points = intermediate risk, ≥ 3 = high risk) and this correlated with two years NRM (non relapse mortality (**Table 11**) [90–93].

The modality of transplant recommended is allogenic after the first complete response (CR1) in high-risk patients (**Table 12**) and in patients with second complete response (CR2) [90].

Autologous HSCT is not recommended for an adult with ALL. It could be possible in high-risk patients with negative minimal residual disease (MRD) that are not considered for allo-HSCT, but there is insufficient data to support this option, including Phi + ALL [91].

7.1 Indication for the different modalities of allo-HSCT

It is preferred a matched sibling donor or an unrelated donor very well matched, these options are considered equivalent in terms of results [91, 92].

Haploidentical transplant is always an option in patients without a matched donor, this type of transplant is nowadays frequently used because it allows almost all patients in need for an allo-SCT to undergo allo-SCT without a matched-donor [96].

7.2 Conditioning

The choice of conditioning is based on the patient's physical status, for those fit without relevant comorbidity the recommended regimens are the combination of fractionated TBI (Total Body Irradiation) 12Gy in 6 fractions, plus

Comorbidity	Points	Comorbidity	Points
Liver disease Liver cirrhosis, bilirubin >1.5xULN, or AST/ALT >2.5xULN	3	Obesity BMI of > 35 for adults	1
Severe pulmonary DLco and/or FEV1 ≤ 65%, dyspnea at rest oroxygen at home	3	Hepatic Mild Chronic hepatitis, bilirubin>ULN to 1.5x ULN, or AST/ALT >ULN to 2.5x ULN	1
Previoussolid malignancy Treated at any time point in thepatient'shistory, excluding nonmelanoma skin cancer	3	Psychiatric disturbance Depression/anxiety requiring psychiatric consult and/or treatment at the time of HCT	1
Heart valve disease Diagnosed (except mitral prolapse)	3	Cerebrovascular Disease Transient ischemic attacks or cerebrovascular accident	1
Moderate pulmonary DLco and/or FEV1 66–80% or minimal stress dyspnea	2	Diabetes Requiring treatment with insulin or oral hypoglycemic	1
Renal Creatinine >2mg/dl, dialysis, or previous kidney transplant	2	Inflammatory bowel disease Crohn's disease or ulcerative colitis	1
Rheumatologic SLE, RA, polymyositis, mixed CTD, and polymyalgia rheumatica	2	Coronary artery disease congestive heart failure, myocardial infarction, or EF of ≤ 50%	1
Peptic ulcer Requiring treatment	2	Arrhytmia Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Previous infection Documented infection or fever of unknown etiology requiring antimicrobial treatment before, during and after the start of conditioning regimen	1	Age ≥ 40	1

EF = ejection fraction; ULN= upper limit of normal, AST = aspartate aminotransferase, ALT = alanine aminotransferase, BMI=body mass index, SLE = systemic lupus erythematosus, RA= rheumatoid arthritis, CTD = connective tissue disease, Dlco = diffusion capacity of carbon monoxide, FEV1= forced expiratory volume in one second.

Table 11.
HCT-Comorbidity Index [89].

Cyclophosphamide (Cy) 120 mg/kg or Etoposide (VP) 60 mg/kg. The regimens with TBI seem to have better anti-leukemic activity than busulfan-based regimens [97].

For elderly patients should be considered reduced conditioning regimens as for patients with contraindications for myeloablative regimens [92].

For patients with an haploidentical donor the used scheme is: Cy 14.5 mg/kg/day IV on days −6 and − 5, fludarabine 30 mg/m^2/day IV on days −6 to −2, and 200 cGy of TBI on day −1, on days +3 and + 4, 50 mg/kg Cy with Mesna [98, 99].

Other regimens for transplant with haploidentical donor recommended by the Acute Leukemia Working Party of EMBT are: 1) Myeloablative regimen TBF (thiotepa 10 mg/kg, fludarabine 150 mg/m2, busulfan 9.6 mg/kg IV. 2) RIC (reduced-intensity chemotherapy) Thiotepa 5 mg/kg and busulfan 6.4 mg/kg. ATG and Cyclophosphamide are used as prophylaxis for Graft versus Host Disease (GVHD) at doses of ATG 10 mg/Kg (total dose), or Cy 50 mg/kg +3 and + 4 [96].

High Risk	
Cytogenetics	Hypodiploidy (< 44 chromosomes) t(9:22) (q34;q11.2):BCR-ABL1 Complex karyotype (5 or more chromosomal abnormalities) t(4;11) (q21;q23) t(8;14) (q24.1q32)
Age	>40 years
High WBC count at diagnosis	>30 x 10^9 in B-ALL >100 x 10^9 in T-ALL
ALL subtypes	T-cell precursor ALL
High-risk genetics	IKZF1 deletion in B precursor ALL, unmutated NOTCH1, Ph-like.
MRD	>1X10^{-4} after two courses of therapy, some groups post-induction.
CNS disease	Central Nervous System involvement
Immunophenotype	Pro-B/early and mature-T
Time to CR	>1 cycle

Table 12.
High Risk Patients [91, 92, 94, 95].

7.3 Maintenance post allo-HSCT

It is recommended for patients with Ph +, maintenance with TKI after allo-HSCT. The optimal treatment duration has not been defined. The described options are continuing the treatment until MRD negativity is confirmed by three consecutive tests or sustained for at least three months, or TKI administration for at least one year of continuous PCR negativity, and if a single positive result, then reset the treatment period [100].

7.4 Status of minimal residual disease before HSCT

It is demonstrated that the presence of MRD positivity at the time of HSCT is a significant risk for relapse after the procedure; this asseveration applies for both B-ALL and T-ALL and suggests that novel therapies are a new option to improve the outcome [101–103].

8. Novel Therapies

8.1 Blinatumomab

It is a bispecific T-cell engager antibody construct that binds simultaneously to CD3-positive cytotoxic T cells and CD19-positive B cells, this reaction allows the patient's endogenous T cells to recognize and eliminate CD19-positive ALL blasts.

It is indicated for the treatment of B- ALL in the first or second complete remission with MRD >/= 0.1% and in B-ALL relapse or refractory in adults and children.

In the TOWER study, eligible patients with pretreated B-ALL were randomly assigned to receive Blinatumomab or Standard Chemotherapy. The overall survival was significantly better in patients treated with Blinatumomab compared with those of the standard group. The median OS was 7.7 months (95% confidence interval [CI], 5.6 to 9.6) in the blinatumomab group versus 4.0 months (95% CI, 2.9

to 5.3) in the chemotherapy group (hazard ratio for death, 0.71; 95% CI, 0.55 to 0.93; p = 0.01 [104].

8.2 Inotuzumab ozogamicin (InO)

It is a humanized anti-CD22 monoclonal antibody conjugated to calicheamicin, a potent cytotoxic antibiotic compound that induces double-strand DNA breaks. It is utilized in patients with relapsed or refractory (R/R) B-ALL [105].

Katarjian H. and cols published a phase 3 trial (INO-VATE ALL) where randomly assigned adults with R/R ALL to receive either inotuzumab ozogamicin or standard intensive chemotherapy. The rate of complete remission was 80.7% in the inotuzumab ozogamicin group than in the standard therapy group, 29.4% $p < 0.001$. In the survival analysis OS of 5.0 months vs. 1.8 months (HR0.45 [97.5% CI, 0.34 to 0.6)]; $p < 0.001$. The veno-occlusive disease occurred more frequently in the InO group [106].

8.3 Tisagenlecleucel

It is a CD19-directed, genetically modified, autologous T-cell immunotherapy. It is prepared from an apheresis collection of the patient's peripheral blood mononuclear cells. The autologous T cells are transduced using a lentiviral vector to express an anti-CD19 chimeric antigen receptor (CAR) [107]. Tisagenlecleucel was the first gene-modified cell therapy approved by the FDA for children and young adults with relapsed or refractory B-cell ALL.

These have proven highly efficient at inducing MRD-negative remissions. A CAR induced remission could offer a window to proceed to allo- HSCT [107, 108].

Maude and cols published this trial of tisagenlecleucel in children with R/R B-ALL, the overall remission rate was 81%. All patients with complete remission were negative for MRD. The rate of relapse-free survival in patients with a response to treatment was 80% at 6 months and 59% at 12 months. Neurologic events occurred in 40% [108].

9. Minimal residual disease (MRD)

In the last decade, the measurement of minimal residual disease has become a necessary tool in the follow-up of patients since its impact on progression-free survival and overall survival has been demonstrated in multiple studies, that leads it to be currently an indicator of treatment for patients with acute leukemia.

There are several ways of measurement of MRD and each one presents different sensitivity as describe: New Generation Sequencing (NGS) present a sensitivity of 10^6; Flow cytometry with a 10^4 sensitivity for cytometers of 6 colors and 10^6 for cytometers of 8 colors or more; PCR for specific genes 10^5 of sensitivity. However, to achieve these sensitivity results, it is necessary to perform them on bone marrow samples considered in morphological remission [89, 109].

We have already discussed the prognostic value of having a negative MRD. The GRAALL group demonstrated that the presence of negative MRD at the end of induction was a better prognostic marker than the conventional ones, like the achievement of CR at first line therapy a transplantation in patients with pediatric schemes [109, 110].

In a meta-analysis published in 2017, including 13,637 patients in total, the progression-free survival for the pediatric group was 77% at 10 years in patients with negative MRD, and 64% for adults, while progression free survival for patients with positive MRD were 32% and 21% respectively [111].

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