Chapter

Overview and Current News in Acute Lymphoblastic Leukemia

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Abstract

The management of acute lymphoblastic leukemia is a challenge in patients of any age range. In the elderly patient, this challenge is further complicated by having to take into account the physical, social, psychological, and emotional factors of this age group, which, together with the complex nature of the disease's biology, give rise to many questions. Although the diagnostic approach of the disease does not differ from that performed in pediatric or young patients, it does in the determination of risk factors and treatment, since many of the determinants of risk have a different value to that assigned in other patients, and, therefore, we cannot apply all available resources in younger patients to facilitate our work. The genetic alterations of ALL are found more frequently in elderly patients, since age is a factor that increases the risk of presenting these alterations. As an example, the prognostic value of the presence of Philadelphia chromosome (t (9:22)) cannot be weighted at the same scale as in pediatric patients. Comorbidities play another important role when it comes to making therapeutic decisions, and there is currently controversy regarding the use of scores designed to determine the physical and physiological status of elderly subjects. Several analyzes have been carried out to define the value and usefulness of these tools in the older patients with ALL; however, work must still be done in this area. The treatment schemes should be adjusted to the needs and specific characteristics of each individual in advanced age. The use of intensive chemotherapy should be discussed within a multidisciplinary team, always considering the benefit of our patients. In the present chapter, the diverse differences in ALL biology will be addressed when compared with those of children and young adults, and with the impact on the different prognostic determinants and their weight at the time of deciding treatment. The need to apply geriatric tools for decision-making and the therapeutic schemes used around the world for elderly people will also be discussed.

Keywords: acute lymphoblastic leukemia, long-term survival, older adults, remission, leukemia-free survival, overall survival, death

1. Introduction

Acute lymphoblastic leukemia (ALL) is a rare disease in the elderly. The prevalence of ALL in patients >60 years of age is reported to be between 16 and 31% of all adult cases. In adults, it represents approximately 20% of all leukemia [1].

The age-adjusted incidence rate of ALL in the United States is 1.58 for every 100,000 persons per year. About 57.2% of the patients diagnosed are under 20 years of age, 26.8% of patients diagnosed are over 45 years of age, and 11% of patients diagnosed are over 65 years of age [2]. The biology of ALL in older patients seems

to be significantly different from that in younger patients and may, at least in part, explain the poor treatment outcome. Immunophenotyping and cytogenetic characteristics are among the most important biological differences in comparison with younger adults. The frequency of pre-B-cell ALL and common ALL is higher, and T-cell ALL subtype is under-represented in elderly populations compared with younger patients. The frequency of the Philadelphia chromosome also seems to increase with age and adversely influences complete remission rate and survival. Few reports on the effectiveness and toxicity of therapeutic programs concerning exclusively older patients with ALL have been published so far and only some of them were prospective studies [3].

In some of the studies, age-adapted approaches have been applied in which protocols processed earlier for younger patients have been adopted for older patients. In such modified protocols, chemotherapy was usually less aggressive, especially if it was given for patients with comorbidities and poor performance status. Consequently, in several studies, elderly patients received suboptimal treatment. Death during induction chemotherapy was observed in 7–42% of the patients in particular reports. The overall response rate varied from 12 to 85%. The median overall survival (OS) durations in patients who received a curative approach ranged from 3 to 14 months and from 1 to 14 months in patients treated with palliative therapy. Poor performance status, comorbidities, and high early mortality during intensive chemotherapy are the main reasons for poor treatment results and short OS time. New therapeutic approaches are necessary to improve the outcome in this age group of patients with ALL [4].

The implementation of tools aimed to determining the safety of treatments in elderly patients based on protocols that have previously been applied and validated in younger patients is a common practice today. A recently identified problem when applying these tasks is the underutilization of treatments with curative purposes in this group. An example of this is the CIRS-G scale, widely used to determine the risk of complications in patients with various comorbidities [4]. This phenomenon has been recorded in various efficacies and safety analyzes of treatment for acute lymphoblastic leukemia in elderly patients based on similar scales, where an important survival difference has been observed between the groups treated for curative purposes and those who received reduced therapy. Of course, comorbidities play an important role in these poor results, which forces us to search for new therapeutic options [5].

The clonal origin of ALL has been established using cytogenetic analysis; restriction fragment analysis in female patients, which are heterozygous for polymorphic genes linked to the X chromosome; and analysis of T-cell receptor or immunoglobulin gene rearrangements. The clinical manifestations are very variable and insidious. The symptoms generally reflect bone marrow failure characterized by four syndromes: anemia, hemorrhage, febrile, and infiltrative. Nearly, half of the patients present with some kind of infectious process at diagnosis. Bone infiltration may produce pain and arthralgia. Additionally, close to half the patients have hepatomegaly or splenomegaly [5].

The long-term survival of older adults with acute lymphoblastic leukemia (ALL) who are intensively treated is about 40% [1]. Hematologic remissions are obtained in over 90% of patients, and the depth of these remissions using flow cytometry and molecular techniques is the subject of current studies. It is likely that, with time, new response definitions based on these tests will be established. The adult patients were divided into age 30 years and 30–60 years, because this seemed clinically relevant, and available data best dealt with these age categories.
However, these divisions are not absolute or evidence-based, and an individual's biologic age and general fitness are of paramount importance. There are no randomized studies in older adults that demonstrate "pediatric" approaches to be

superior, and indeed, the single-arm studies are still small scale in this age group, with insufficient follow-up. Much is unknown, but the wide variety of trials being conducted in adults with ALL is heartening [6].

2. Physiopathology

The development of ALL is driven by successive mutations that alter cellular functions promoting

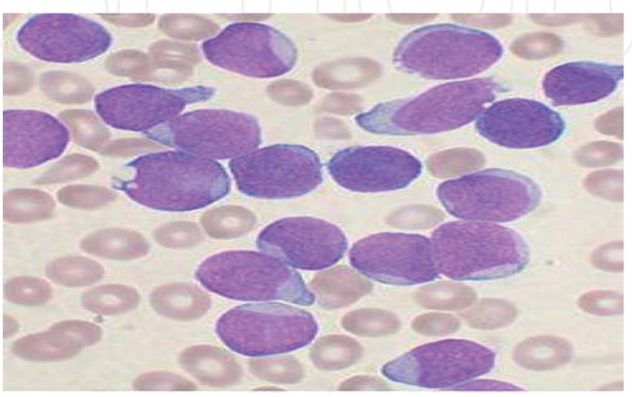
- greater ability for self-renewal,
- greater proliferation,
- blockage of differentiation, and
- resistance to apoptotic signals.

Different hereditary DNA repair disorders can play an important role in the induction of this disease. Furthermore, mutagenic environmental agents, which can be physical (ionizing radiation), chemical (benzene), and biological (HTLV-1), can also be involved. However, in most cases, there are no identifiable etiologic agents. The precise pathogenic events that lead to the development of ALL are unknown. About 5% of the cases are associated with genetic predisposition syndromes. This is the case for children with Down syndrome, who have a 10–30 times greater risk of leukemia and present genetic abnormalities such as hyperdiploidy and t (12; 21) [ETV6-RUNX1], +X, del (9), and alteration in CCAAT//enhacer-binding protein beta (CEBPD). It has been demonstrated that the fusion of P2RY8-CRLF2 and the activation of JAK mutations contribute to 50% of the ALL cases in patients with Down syndrome. Ninety percent have a deletion of IKZF12015. The disorders associated with chromosomal fragility that have been found to predispose to ALL include ataxia-telangiectasia, Nijmegen syndrome, and Bloom syndrome [7]. Patients with ataxia-telangiectasia have 70 times greater risk of leukemia and 250 times greater risk of lymphoma, particularly of T cells. The causal gene, ataxia-telangiectasia mutated (ATM), encodes a protein implicated in DNA repair and regulation of cellular proliferation and apoptosis [2, 7, 8]. Complete genome sequencing studies have identified a number of common allelic variants in four genes (IKZF1, ARID5B, CEBPE, and y CDKN2A) associated with infant ALL. The allelic variant inherited can affect the response to treatment. In utero exposure to X-rays for diagnostic use can confer a slight increase in risk for ALL, which positively correlates with exposure intensity. Data exist that support a causal role for polymorphisms in genes that encode antioxidant enzymes (for example: glutathione S-transferase, nicotinamide adenine dinucleotide phosphate (NADPH), quinone oxidoreductase), folate metabolic enzymes (serine hydroxymethyltransferase and thymidylate synthase), cytochrome 450, methylenetetrahydrofolate reductase, and cell cycle inhibitors [3, 5, 8, 9]. Specific fusion genes have been identified in leukemia, the most noteworthy being KMT2A/AFF1 (also known as MLL-AF4) and ETV6-RUNX1 or TEL-AML1; additionally, there is hyperploid and rearrangements of immunoglobulin or T-cell receptor genes. The acquired genetic anomalies are a hallmark, 80% of all cases contain cytogenetic or molecular lesions with abnormalities in chromosome number (ploidy) and structure. The mechanisms involved include aberrant expression of oncoproteins, loss of tumor suppressor genes, and chromosomal translocations, which generate fusion genes that encode transcription factors of active kinases. A

single genetic rearrangement is not enough to induce leukemia. Cooperative mutations are necessary for leukemic transformation and include genetic and epigenetic changes in regulatory growth pathways. Candidate genes identified include deletion of the tumor suppressor locus CDKN2A/CDKN2B and NOTCH1 mutations in T cells. The use of single nucleotide polymorphism (SNP) microarrays suggests that genomic instability is not characteristic of most cases. There is a great variation in the number of alterations in different subtypes of leukemia. The infant cases with rearrangements of the MLL gene had less than one copy number alterations (CNA) per case, suggesting that few genetic lesions are required. Conversely, cases with ETV6-RUNX1 [25] and BCR-ABL1 had more than six CNAs, some containing more than 20 lesions, which support the concept that despite the initiating events that may occur in early infancy, additional lesions are required for the subsequent development of ALL. The lymphoid transcription factor PAX5 encodes a protein involved in evolution and fidelity of the B-cell lineage. The second most frequently affected gene was IKZF1, which encodes the protein IKAROS, required for lymphoid differentiation. IKZF1 is absent in most cases with BCR-ABL1. Approximately, half of the patients expressing BCRABL1 also had deletions in CDKN2A/B and PAX5. This finding suggests that alterations in different signaling pathways are needed to induce leukemia [15]. A special role in this disease is played by the presence of the Philadelphia chromosome t (9; 22), which expresses the BCR-ABL fusion gene, and this has diagnostic, prognostic, and therapeutic implications [3, 6–11].

3. Morphologic diagnosis

The bone marrow aspiration test is fundamental to confirm the presence of lymphoblasts (by morphology and/or cytochemistry with special stains that include a negative MPO in 100% of cells, Periodic Acid-Shiff (PAS) (+) in 70–80%, and acid phosphatase (+) in the case of T lymphoblast). The WHO suggests greater than 20% as diagnosis criteria (if the percentage is lower, one must search for extramedullary disease at the nodal level to differentiate from the diagnosis of lymphoblastic lymphoma). The bone marrow aspiration is hypercellular 95–100% of the time; however, in those cases where the aspirate is "dry" (packed bone marrow), which corresponds to 1–2% of the cases, a bone biopsy must be carried out for histopathological confirmation. Based on morphology, the French-American-British (FAB) classification identifies three types of ALL [7, 8, 12].



The first step to integrate the diagnosis of ALL is the morphological identification of lymphoblasts. For this, it is necessary to perform a bone marrow aspirate and be observed directly under a microscope by an expert in hematology, which can be supported in other tests like special stains, as in the case of myeloperoxidase, which must be negative in all the malignant cells observed; PAS staining, which is considered

positive for ALL when observed in 70–80% of cells with malignant morphology and acid phosphatase, which is used for T-cell differentiation. Regarding manual cell counting, it is necessary that the presence of 20% or more cells with malignant characteristics, as indicated by the criteria of the WHO classification, in case this criterion is not met, can be replaced by others such as the documentation of extramedullary disease. It is important to specify that most of the times, we may have difficulties in trying to obtain the sample for the bone marrow aspirate, since the large number of cells within the medullary space condition the presence of the phenomenon of "dry" aspiration; in these cases, we must carry out bone biopsy in a mandatory manner.

3.1 Images ALL

The French-American-British (FAB) classification that was used commonly earlier includes:

- L1—around 25–30% of adult cases and 85% of childhood cases of ALL are of this subtype. In this type, small cells are seen with:
  - regular nuclear shape
  - homogeneous chromatin
  - small or absent nucleolus
  - scanty cytoplasm
- L2—around 70% of adult cases and 14% of childhood cases are of this type. The cells are large and/or have varied shapes with:
  - irregular nuclear shape
  - heterogeneous chromatin
  - large nucleolus
- L3—this is a rarer subtype with only 1–2% cases. In this type, the cells are large and uniform with vacuoles (bubble-like features) in the cytoplasm overlying the nucleus.

In an initial effort, the French-American-British (FAB) was given the task of subclassifying this type of leukemia according to various morphological characteristics in order to try to determine the behavior and prognosis of each type based on its morphology; this is how the FAB morphological classification was born, which subdivides the ALL into three types:

- L1: this subtype is characterized by presenting cells with a regular nucleus, homogeneous chromatin, small or absent nucleoli, and scarce cytoplasm. It represents the majority of the ALL in children observed in up to 85%, while in adults, it is seen between 30% and 70% of the times.
- L2: unlike the previous one, this subclassification is seen mostly in adults (70%) and its morphology is opposite to L1: chromatin is heterogeneous, the nucleus irregular, and with multiple nucleoli.

- L3: the least frequent of the three, is reported between 1 and 2% of the time. Its main characteristic is the large number of vacuoles (bubbles) that these cells present in their cytoplasm. The shape of the nucleus may vary.

3.2 Revised version of FAB

WHO proposed a classification of ALL that was to be the revised version of the FAB classification.

This used the immunophenotypic classification that includes:

- Acute lymphoblastic leukemia/lymphoma or formerly L1 and L2 this has subtypes including:
  - precursor B acute lymphoblastic leukemia/lymphoma: this has genetic subtypes including t(12,21)(p12,q22) TEL/AML-1, t(1,19)(q23;p13) PBX/E2A, t(9,22)(q34;q11) ABL/BCR and T(V,11)(V;q23) V/MLL
  - precursor T acute lymphoblastic leukemia/lymphoma
- Burkitt's leukemia/lymphoma or formerly L3
- biphenotypic acute leukemia

The WHO performed a new categorization of acute lymphoblastic leukemia, based on cytogenetic alterations present in this disease. This classification considered what was previously described in the FAB classification being possible to make an indirect correlation between the morphological findings and the alterations listed in the categories of the WHO classification. In this way, those leukemias that are traditionally classified in the FAB groups L1 and L2 can belong to the group of leukemia of precursors B with alterations such as: t (12; 21) (p12, q22) TEL/AML-1, t (1; 19) (q23; p13) PBX/E2A, t (9; 22) (q34; q11) ABL/BCR, and T (V, 11) (V; q23) V/MLL. Those traditionally classified as FAB L3 correlate with Burkitt's leukemia/lymphoma; T-cell leukemias are still an independent group and are considered another group where those that meet criteria for two different lineages are included.

4. Lineage

The proportion of B-lineage ALL is higher in patients older (75–89%) than 60 years compared to patients younger (59–66%) than 60 years. Accordingly the incidence of T-ALL is lower in older (8–12%) compared to younger (29%) patients [5–7]. A population-based study showed that cytogenetics were less frequently attempted in older (73%) compared with younger (85–91%) patients. The proportion of patients with Philadelphia chromosome positive (Ph+) t(9;22), t(8;14), t(14;18), or complex aberrations increased with age [11]; Ph+ ALL accounted for 24–36% in older patients vs. 15–19% in younger patients. Considering the consequences resulting from diagnostic characterization, it should be self-evident that complete diagnostic characterization is required in all patients with ALL, regardless of age [13, 14].

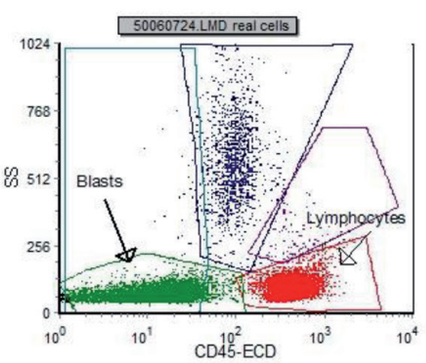
There are several important differences in the biology of lymphoblastic leukemia in patients over 60 years compared to those under this age, although we know that B-lineage leukemia is the most common in adults, the frequency between both groups can vary reporting a little more frequent in those over 60 years (75–89%/59–66%), another more radical difference is the presentation of leukemia of T lineage, which is

more common in adults under 60 years (29%) than in elderly patients (12%) [5–7]. Cytogenetic alterations of importance for the prognosis, such as Philadelphia chromosome (Ph+) t (9; 22), t (8; 14), t (14; 18), or complex karyotype are observed more frequently as the patient's age increases [11]. Although the search for cytogenetic alterations is crucial to define the risk and possible response to treatment of acute leukemia, this analysis is not carried out in most elderly patients (73%), contrary to the young patients, who have available cytogenetic studies in up to 91%. The importance of this difference lies in the fact, already mentioned, of the increase in the frequency of high-risk alterations, as an example Ph+ ALL can be found in up to 36% of cases, which have different therapeutic approaches to those that do not suffer from this alteration [13, 14].

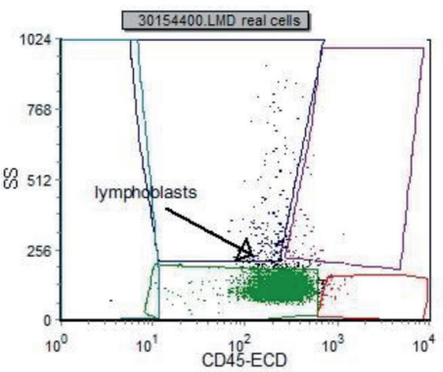
As in other B-cell malignancies, monoclonal antibodies to CD20 or CD228 are being tested as adjuncts to chemotherapy in the hope that they will increase remission depth and improve survival without increasing hematologic toxicity. About 60–80% of B-cell ALL patients express these antigens at variable densities, but there is little evidence linking antigen expression to response. CD20 expression may be associated with a worse prognosis, so it is logical to investigate CD20 antibodies in randomized trials, and it may improve the outcome [15, 16].

4.1 Immunophenotyping

Blasts in pre-B ALL can be initially identified using an SSC vs. a CD45 plot. These blasts have low SSC (many times smaller than normal lymphocytes) and dim to negative CD45.



Example peripheral blood with CD45 negative B lymphoblasts and characteristically small (low SSC)

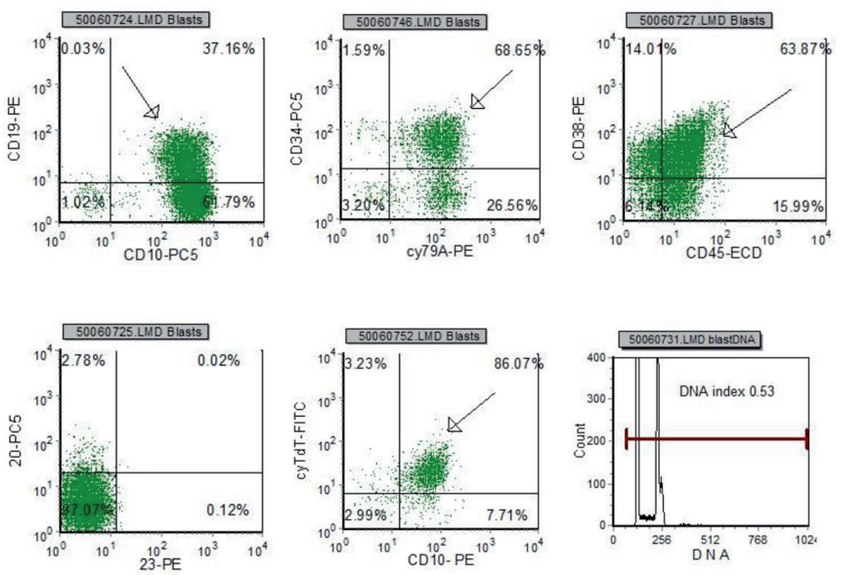


Example bone marrow with CD45 dim B lymphoblasts.

Once the blasts are identified and gated, the following markers are useful in the classification of pre-B ALL:

Marker	Prevalence
CD10	89%
CD13	5%
CD19	100%
CD20	24%
CD22	69%
CD33	31%
CD34	76%

Marker	Prevalence
CD45 (bright)	2%
CD45 (moderate)	33%
CD45 (dim)	36%
CD45 (negative)	29%
CD56	36%
CD79a	88%
CD117	0%
Cytoplasmic IgM	22%
HLA Dr	98%
TdT	91%



Pre B ALL cells characteristically coexpress CD10 and CD19. In addition, CD20 and CD23 (other B cell

Expression of CD34 and TdT indicates immaturity and is characteristic in pre B ALL. Cytoplasmic expression of CD79 confirms B cell lineage.

CD38 is an expression of immaturity. The ploidy as seen by the DNA Histogram, indicates a hypodiploidy (DI=0.53)

Included are marking prevalences.

The phenotype of the blasts is an independent prognostic parameter. B-ALL is subdivided into following:

- *Early Pre-B ALL*: TdT+, CD19+, CD10-
- *Common ALL*: CD19+, CD10+/CALLA+
- *Pre-B ALL*: CD10+/−, CD19+, HLA DR+, cytoplasmic IgM+
- *Mature B ALL*: CD10+, CD19+, CD20+, CD22+, surface IgM+

4.2 Immunophenotype of T-lineage ALL

T-cell ALL constitutes approximately 25% of all adult cases of ALL. T-cell markers are CD1a, CD2, CD3 (membrane and cytoplasm), CD4, CD5, CD7, and CD8.

CD2, CD5, and CD7 antigens are markers of the most immature T cells , but none of them is absolutely lineage-specific, so that the unequivocal diagnosis of T-ALL rests on the demonstration of surface/cytoplasmic CD3. In T-ALL, the expression of CD10 is quite common (25%) and not specific; CD34 and myeloid antigens CD13 and/or CD33 can be expressed too. Recognized T-ALL subsets are the following: pro-T EGIL T-I (cCD3+, CD7+), pre-T EGIL T-II (cCD3+, CD7+, and CD5/CD2+), cortical T EGIL T-III (cCD3+, CD1a+, and sCD3+/−), and mature-T EGIL T-IV (cCD3+, sCD3+, and CD1a−). Finally, a novel subgroup that was recently characterized is represented by the so-called ETP-ALL (early-T precursor), which shows characteristic immunophenotypic features, namely lack of CD1a and CD8 expression, weak CD5 expression, and expression of at least one myeloid and/or stem cell marker [17].

4.3 Mixed phenotype acute leukemia

With currently refined diagnostic techniques, the occurrence of acute leukemia of ambiguous cell lineage, i.e., mixed phenotype acute leukemia (MPAL) is relatively rare (<4%) [19]. These cases express one of the following feature: (1) coexistence of two separate blast cell populations (i.e., T- or B-cell ALL plus either myeloid or monocytic blast cells), (2) single leukemic population of blast cells co-expressing B- or T-cell antigens and myeloid antigens, and (3) same plus expression of monocytic antigens. For myelo-monocytic lineage, useful diagnostic antigens are MPO or nonspecific esterase, CD11c, CD14, CD64 and lysozyme; for B-lineage, CD19 plus CD79a, cytoplasmic CD22 and CD10 (one or two of the latter according to staining intensity of CD19); and for T-lineage, cytoplasmic or surface CD3. Recognized entities include Ph+ MPAL (B/myeloid or rarely T/myeloid), t(v;11q23); MLL rearranged MPAL, and genetically uncharacterized B or T/myeloid MPAL. Very rare cases express trilineage involvement (B/T/myeloid). Lack of lineage-specific antigens (MPO, cCD3, cCD22) is observed in the ultrarare acute undifferentiated leukemia. In a recent review of 100 such cases, 59% were B/myeloid, 35% T/myeloid, 4% B/T lymphoid, and 2% B/T/myeloid. Outcome was overall better following ALL rather than AML therapy [7, 16, 18, 19].

4.4 NK cell ALL

CD56, a marker of natural killer (NK) cell differentiation, defines a rare subgroup of about 3% of adult ALL cases, which often display other early T-cell antigens, CD7 CD2 CD5, and sometimes cCD3. True NK ALL is very rare (TdT+, CD56+, other T markers negative, and un-rearranged TCR genes). This diagnosis rely on the demonstration of early NK-specific CD94 or CD161 antigens [18, 19].

4.5 Diagnostic cytogenetics

Cytogenetics represents an important step in ALL classification. Conventional karyotyping can be helpful in the identification of recurrent translocations, as well as gain and loss of gross chromosomal material; however, the major limitation of this technique is that in some cases, leukemic cells fail to enter metaphase. However, fluorescence in situ hybridization (FISH) can enable the detection and direct visualization of virtually all investigated chromosomal abnormalities in ALL, with a sensitivity of around 99%. Finally, array-comparative genomic hybridization (array-CGH, a-CGH) and single nucleotide polymorphisms (SNP) arrays can permit the identification of cryptic and/or submicroscopic changes in the genome. Karyotype changes found in ALL include both numerical and structural alterations, which have profound prognostic significance. With these premises in mind, the

karyotype changes that occur in ALL can be roughly subdivided in those associated, respectively, with a relatively good, intermediate, and poor prognosis. However, it must be kept in mind that the incidence of certain aberrations is very low, and that for some of them, the prognostic impact can be strongly affected by the type and intensiveness of therapy administered [8, 20].

5. Clinical status

Features associated with large tumor mass or rapid progression, such as high white blood cell count, mediastinal tumors, or other organ involvement, appear to be less common in older patients. Even "smoldering" ALL is observed in some cases. Most studies report a lower proportion of males among older ALL patients. Secondary ALL after myelodysplastic syndromes or other malignant disease may become increasingly important, particularly in older patients; so far, very limited data are available. Performance status often deteriorates in older patients with onset of disease. In two studies, 30–43% of patients older than age 60 years vs. 18–22% of younger patients had a performance status of 2 or more. Therefore, it is important not only to consider the current general condition in newly admitted older ALL patients but also to discern their status before the onset of leukemia-associated symptoms [17, 21].

The determination of the clinical status at the moment of making the diagnosis provides us with information about the global state of the patient, so that we can make better decisions. This varies in comparison with the younger groups in questions such as the low initial presentation of large tumor mass, identified by the elevated white blood cells count in the peripheral blood, the rare extranodal affection and even in some cases being observed, apparently "benign" clinical presentation with low tumor burden. A smaller proportion of male patients in this group have also been observed as compared with younger groups. Secondary leukemia, which we define as that which occurs after a premalignant pathology, most frequently myelodysplastic syndrome, or after treatment of nonhematological neoplasms, is a condition that has been observed more and more frequently in recent years. However, there is little data to help us determine its nature. It is important to assess these patients comprehensively in order to determine their physical and health status prior to the onset of symptoms related to leukemia [17, 21].

6. Comorbidity

Of older ALL patients, 60–70% suffer from comorbidities, but most studies did not refer to validated scoring systems. The German multicentre study group for adult ALL (GMALL) identified comorbidities according to the Charlson score in 84% of the patients older than 55 years, with diabetes (46%), vascular disease (18%), heart failure (15%), and chronic lung disease (12%) being the most frequent. In addition, renal insufficiency, anemia, osteoporosis, dementia, and depression are probably the most relevant comorbidities for potential adjustment of treatment. About 8–16% had a history of prior malignant disease. I recommend a systematic evaluation and documentation of comorbidities based on a checklist or a score, since this is essential for planning an optimal treatment strategy [4, 5, 18, 23].

Comorbidities in elderly patients with ALL require a specialized and detailed approach. The German multicentre study group for adult ALL (GMALL) recommends the use of the Charlson scale for the determination of risk due to comorbidities; this assessment must be done in an integral manner, together with the physics, biochemistry, and cytomolecular evaluation of the disease [4]. Multiple systemic

diseases can afflict elderly patients with ALL: diabetes, hypertension, heart failure, and renal failure are some of the most frequently reported in the various studies conducted. Age-specific conditions such as dementia or osteoporosis that can negatively impact the patient's performance before and after treatment should not be left aside. It is also important to evaluate, monitor and, if necessary, treat alterations in the emotional state of the elderly patient, since depression and anxiety are not infrequent conditions in this group [5, 18, 22].

7. Prognostic factors in older ALL patients

Now, we have a better understanding of the factors that determine survival, but these will require reexamination as we introduce novel therapies. Cytogenetic findings such as Philadelphia chromosome positivity, t (4; 11), complex cytogenetic abnormalities (more than five chromosomal changes), and low hypodiploidy/near triploidy result in inferior survival. Some of these changes are more common in older adults. Other conventional factors such as increasing age, high white blood cell count, and B-cell disease (rather than T-cell disease) still hold true and predict higher failure rates with standard chemotherapy. However, many of these factors are also associated with a higher relapse rate after allografting, and it is not necessarily the case that bone marrow transplantation (BMT) is the solution for patients with adverse prognostic features. Combining these factors may allow individualization of therapy, a prospect not previously possible in this rare condition. As well as undertreating patients with ALL with chemotherapy that is likely to fail, prognostic factors should be used to avoid over treating better prognosis patients with allogeneic transplants that have a high upfront risk and may result in chronic graft-versus host disease (GVHD), infertility, and secondary malignancy. Chemotherapy and transplant have complementary roles in ALL management, and a pragmatic approach is required to deliver the best outcomes. The role of BMT is likely to increase, especially with the promising results of reduced-intensity allografting, but conversely, the use of BMT should be reduced if advances in nontransplant therapy improve cure rates [11, 17, 20, 23].

Increasing age itself is one of the most relevant prognostic factors for outcome of ALL from childhood to old age. Since older patients show opposite problems, namely higher mortality and relapse rates, prognostic factors for both have to be analyzed. Prognostic factors for relapse risk in younger ALL patients are probably also valid in older patients, such as early and mature T-ALL, pro-B ALL, elevated white blood cell count, and Ph+ ALL; however, their predictive value is somewhat diluted by mortality risks. Evaluation of minimal residual disease (MRD) has demonstrated that persistence of MRD is associated with a relapse rate above 90% in younger patients despite continued intensive chemotherapy. Few data on the prognostic impact of MRD are available in older patients. In one study, only 11% of the older patients with molecular failure after first consolidation remained in complete response (CR) compared with 68% of those with molecular remission. In older patients with less intensive therapy, a higher rate of MRD persistence and an even poorer outcome can be expected. Therefore, prospective evaluation of MRD in older patients is essential to identify those who could benefit from alternative experimental treatments, if they were available [18–20, 24].

Some poor prognosis factor applicable to young patients can also be in elderly patients, which tells us of the profound impact they have on the biology of the disease: the T lineage and the positive Phi chromosome are a pair of these. The persistence of positive minimal residual disease is directly related to an increased frequency of relapse after remission; it is estimated that young patients with positive MRD will relapse up to 90% despite receiving intensive CT. We do not have

such exact estimates of how much the likelihood of relapse increases when this phenomenon occurs in older patients, but it has been estimated in some studies that only 11% of these who presented with MRD positive remain in response to the disease. Prospective studies that answer these questions are required; however, it is necessary to determine MRD in elderly patients as part of the management and surveillance protocols [18–20, 23].

In the GMALL study for older patients, we identified comorbidity score, age, and performance status before onset of leukemia as prognostic factors with significant impact on early mortality. Interestingly, Eastern Cooperative Oncology Group (ECOG) status of 2 or more was documented in 7% of the patients before onset of leukemia-associated symptoms, but in 38% after onset. The strong correlation of performance status with mortality was confirmed by others.

For assessing prognosis in an older ALL patient, it is essential to identify features suitable for predicting high risk of early mortality resulting from complications. These features can help determine whether a patient has any chance of benefiting from intensive treatment. For this purpose, I would consider performance status before onset of leukemia, comorbidities, and geriatric assessment and would not rely on scores, which are calculated on the basis of historical patient cohorts.

In addition, prognostic factors for response to antileukemic treatment and relapse risk must be considered. Because of the lack of confirmed prognostic factors for older ALL patients, my approach would be to take known prognostic factors for younger patients into consideration, but to focus on MRD evaluation as an individual prognostic feature that can cover the impact of biologic factors and also treatment intensity, compliance, and other unknown features [21, 26].

In the case of patients with characteristics that could increase the risk of early mortality when starting treatment, we must be careful in how to approach this last parameter. Several groups dedicated to the analysis of prognostic factors in special groups of patients have determined a series of variants and elements that could guide the clinic when defining the risk of death of his patient. The GMALL group determined, in a prospective analysis, that the low physical status (ECOG status of 2 or more) prior to the onset of leukemia symptoms correlates with earlier mortality and in those patients who already have a diagnosis, this score is seen duplicated at the beginning of the symptomatology. To be able to carry out a complete evaluation of elderly patients, it is necessary to apply tools that are useful in most clinical scenarios and that confer a high degree of reliability with respect to their predictive power of prognosis. It is therefore necessary to apply validated geriatric scores and specific scores of the patient for known morbidities in order to achieve the most complete vision possible before the diagnosis, in order to guide the treatment and its intensity [21].

In addition to this, we must define what prognostic factors for relapse should be applied to these patients after treatment is initiated. Although several of them already known with importance in young group can also be applied to elderly patients, it should be determined which are more specific for this last group [26].

7.1 Philadelphia ALL

One-quarter of all adults have Philadelphia chromosome, and the incidence increases with age. Until the results of recent studies in older patients became available, most patients with Philadelphia ALL were managed with intensive chemotherapy and a tyrosine kinase inhibitor (TKI). Imatinib has improved the CR rate in a number of trials to 90% and makes more patients eligible for transplant. Imatinib-resistant mutations are increasingly reported, and these should be sought in relapsed and refractory patients. Dasatinib, which inhibits tyrosine and src kinases, holds considerable promise. It may also be effective in CNS disease. There are no

randomized comparisons with imatinib, although it is a more potent inhibitor of tyrosine kinase in vitro. Recent studies from Italy and France with dasatinib alone in older patients have achieved very high remission rates with encouraging short-term survival. Good minimal residual disease (MRD) responses correlated with outcome. Data regarding the combination of dasatinib and intensive chemotherapy are lacking. It is possible that less conventional induction therapy may be required and that allogeneic stem cell transplantation (SCT) may not be mandatory. The remarkable effectiveness of TKI therapy, in some studies without chemotherapy or allografting, has made us consider de-escalation of therapy, but the long-term results of these less intensive approaches are unknown, and allografting is the only known cure. The effect of pretransplant MRD status on outcome is unclear [27, 28].

A study of 267 patients (prior to the TKI era) showed allogeneic transplant to be superior to chemotherapy, with 44 and 36% surviving 5 years after sibling and unrelated donor SCT, respectively. However, only 28% of patients proceeded to a CR1 allograft, reducing its impact, and making it important that we improve no transplant therapy (and improve access to transplant). The Minneapolis group reported 50% survival in 14 patients who received reduced-intensity conditioning (RIC) allografts from cord or sibling donors. TKIs were used only for morphologic or molecular relapse posttransplant. Studies of TKI posttransplant that examine dose, duration, and molecular response are urgently required; this is the subject of studies from the German and UK groups that are soon to be reported [28, 29].

7.2 Therapy

The goal of remission induction therapy is to achieve remission without undue toxicity with a hematologic recovery that permits further therapy to be promptly given. Most regimens use prednisolone or dexamethasone, vincristine, daunorubicin, and asparaginase, with later exposure to cyclophosphamide and Ara-C (cytosine arabinoside or cytarabine). Hyper-cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD), which does not contain L-asparaginase, achieves high complete remission (CR) rates in newly diagnosed patients and is a reasonable alternative for induction therapy, but has not been shown to be superior to more traditional induction protocols. Dexamethasone is preferred to prednisolone because of superior lymphocytotoxicity, better central nervous system (CNS) penetration, and fewer thromboembolic events; these data are derived from pediatric studies. Poly(ethylene glycol)-asparaginase may be associated with more effective asparagine depletion, and this in turn may lead to better outcomes. But this requires a randomized comparison. The safety and optimum dose of this drug require further study in adults [25, 26, 30].

Population-based study registries give an impression on the overall outcome of unselected older ALL patients. Survival rates in patients aged 60 years were 12% at 5 years in Northern England. For those aged between 65 and 74 years, survival was 25% in Sweden where outcome further decreased to 10% in patients aged 74 years. Five-year OS in patients aged 60–69 years increased from 8% in the years 1992–2001 to 20% in the years 2002–2011, whereas only marginal improvements from 5 to 10% were observed for patients aged 70 years. Palliative treatment: some 30–70% of the older patients are allocated to palliative therapy mainly due to poor performance status at diagnosis. Most studies have shown an advantage of more intensive therapy such as higher CR rate, lower early death, better remission duration, and median survival compared with palliative treatment according to protocols for adult ALL patients. The majority of published data are based on results reported for the subgroup of older patients treated within protocols designed for adult ALL in general. One large data set confirmed considerable mortality of 18%. The conclusion

that induction therapy designed for younger patients may be too intensive for older patients. Patients may acquire severe infections, nonpredefined treatment modifications occur frequently, and treatments may be interrupted or even stopped due to severe complications. Overall, potential conclusions from these studies are very limited. Prospective studies of protocols for older ALL patients specifically designed for older ALL patients have the theoretical aim to provide a chance of cure on the one hand and to limit toxicity, early mortality, and hospitalization duration on the other hand, and the therapy maintains as much quality of life as possible. One central question is whether and/or which anthracycline has to be included in induction regimens for older patients, because these drugs contribute considerably to bone marrow toxicity [5, 6, 15, 31]. One approach is the use of idarubicin in induction, based on a potentially lower cardiac and hepatic toxicity. The results of liposomal anthracyclines in elderly ALL are not convincing so far. Asparaginase is an essential compound in the treatment of ALL. The PETHEMA group reported the results of an intensive induction regimen, including asparaginase for older ALL patients. The early death rate, mainly due to infection, was rather high (36%) and was reduced after omission of asparaginase and cyclophosphamide. A high early mortality rate (29%) and a number of complications including infections (71%), cardiac toxicity (18%), and hyperglycemia (24%) were also observed in another trial utilizing asparaginase during induction therapy. Furthermore, a pediatric-based regimen using pegylated asparaginase during induction in older patients revealed grade 3–4 bilirubin increases in 33% of the patients. Thrombosis and pancreatitis are other relevant toxicities of asparaginase. Altogether, there is some evidence that the use of asparaginase during induction therapy may be associated with increased risks in older patients. Therefore, it would be advisable to start asparaginase in older patients later during consolidation. The majority of complications in older ALL patients is observed during induction; thus, there is still space for intensification of consolidation therapy [14, 23, 32]. Based on this assumption, a consensus treatment protocol for older patients with ALL was defined by the European Working Group for Adult ALL (EWALL). The 4-week, pediatric-based induction comprises dexamethasone, vincristine, and idarubicin in phase 1 and cyclophosphamide and cytarabine in phase 2. Consolidation consists of six alternating cycles with intermediate-dose methotrexate combined with asparaginase and high-dose cytarabine, followed by maintenance. The median age at enrollment was 66 (56–73) years with 22% at 70 years. The incidence of grade 3–4 cytopenias was 90%, and infections during phases 1 and 2 of induction occurred in 16 and 25% of the patients, respectively. Toxicities were less pronounced during consolidation, and asparaginase was well tolerated. CR, survival, and continuous CR rates after 1 year were 85, 61, and 49%, respectively. Another report based on the same backbone showed CR rates of 74% and an OS of 30% at 2 years [18, 20, 33]. The authors also observed grade 3–4 infections in 62% of the patients during induction therapy with a median duration of neutropenia of 24 days, whereas consolidation was far better tolerated even when including the use of asparaginase [18, 20, 23, 34]. The GMALL has conducted thus far the largest prospective trial specifically designed for older patients with Ph/BCR–ABL-negative ALL. Pediatric (Berlin-Frankfurt Munster)-based, dose-reduced induction therapy with idarubicin, dexamethasone, vincristine, cyclophosphamide, and cytarabine was followed by alternating consolidation cycles for 1 year and maintenance. Patients with CD201 ALL received rituximab in combination with chemotherapy. The median age of this cohort was 67 (55–85) years. In 268 patients, the CR rate was 76%, early death rate 14%, mortality in CR 6%, continuous remission 32%, and survival 23% at 5 years. Patients aged 75 years with an Eastern Cooperative Oncology Group performance status below 2 had an 86% CR rate, 10% early death, and 36% survival at 3 years. Interestingly, the replacement

of triple intrathecal therapy during induction resulted in a reduced early mortality. Moderate intensification of consolidation as in the EWALL regimen, with inclusion of high-dose cytarabine and intermediate-dose methotrexate and native *Escherichia coli* asparaginase was tolerated [24, 26, 30].

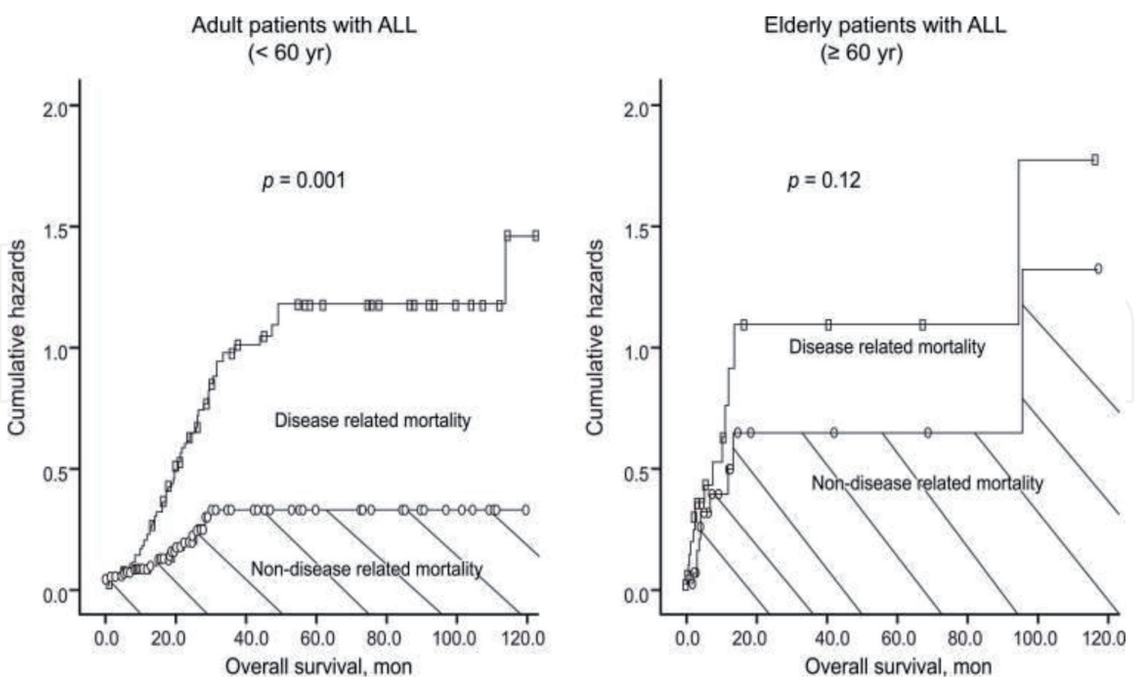
Overall, mortality in CR was 6% only. Overall, pediatric-based regimens in ALL are undoubtedly successful and should be scheduled with prospectively defined adaptations with respect to tolerability in older patients. The most important modification of induction therapy in older patients is probably the omission of asparaginase, and the flexible, reduced dose of anthracyclines. In consolidation, intensified treatment should be attempted, and during this treatment phase, even asparaginase may be surprisingly well tolerated at moderate doses [29, 34]. In this treatment, patients aged 55–70 years and 70–75 years tolerated pegylated asparaginase at dose levels of 1000 and 500 U/m^2, respectively, as single-drug interim therapy during consolidation. Combination with high-dose methotrexate will be further explored and careful use is recommended in patients with preexisting liver disease. [23, 24, 26, 30, 35]. Nowadays, older patients with Ph+ ALL may have a better chance to achieve a CR than patients with Ph+ ALL. The use of TKIs upfront is most promising. The GMALL conducted a first randomized study to evaluate the efficacy of imatinib single-drug induction compared with chemotherapy. The remission rates were 96 and 50%, respectively. Only 11% of the patients achieved a molecular remission. A follow-up including nonrandomized data yielded a CR rate of 88% in 121 patients, together with a 22% 5-year survival rate. The Gruppo Italiano Malattie Ematologiche dell'Adulto trial used imatinib (800 mg) with prednisone for induction, followed by imatinib single-drug treatment. The CR rate, survival, and disease-free survival were 100, 74, and 48%, respectively, after 1 year. A subsequent trial with dasatinib (140 mg) and prednisone, followed by dasatinib single-drug treatment, was not specifically designed for older patients (range, 24–76 years). The CR rate was 92% and survival was 69% at 20 months. Postremission therapy was at the discretion of the treating physician and 14 of 19 patients with TKI monotherapy relapsed with a high frequency of T315I mutations [31, 33, 35]. Another trial was based on a rotating schedule with 6 weeks of nilotinib treatment alternating with imatinib treatment. In 39 patients, the CR rate was 94% and the OS at 1 year was 79%. Nearly, all relapsed patients in this trial showed mutations associated with TKI resistance. The largest prospective study so far in older patients with Ph+ ALL used an EWALL chemotherapy backbone with vincristine, dexamethasone, and dasatinib (140 mg) for induction. Consolidation and maintenance according to the EWALL backbone was combined with intermittent dasatinib applications. In 71 patients, the CR rate was 96%. The regimen was feasible and the survival after 5 years of follow-up was 36%, which is promising. Persistent MRD above 0.1% after induction and consolidation was associated with poorer remission duration of only 5 months. A subsequent EWALL trial with a similar backbone but with nilotinib (400 mg twice daily) instead of dasatinib was started subsequently. Again, a high CR rate of 97% was reported. About 30% of patients achieved a complete molecular remission after induction. Overall, there is increasing evidence that second-generation TKIs in combination with dose-reduced chemotherapy can induce very high CR rates with low mortality in older patients. The rate of molecular remissions appears to be higher compared with imatinib-based regimens. Moderate intensive consolidation therapies in combination with TKIs are tolerated well. Long-term results have to be assessed after 5 or more years and show a still high rate of relapses. New approaches may include reduced intensity stem cell transplantation (SCT), MRD-based change of TKIs, or use of new immunotherapies [23, 36, 37].

In other study, 127 patients with ALL were enrolled including 26 elderly patients (≥60 years) and 101 younger adult patients (<60 years). The median follow-up durations were 6.0 months (range, 0.4–113.2) in the elderly patients

and 21.7 months (range, 1.0–122.7) in the younger patients. The median age of the younger patients with ALL was 30 years (range, 15–58), whereas that of the elderly patients with ALL was 65 years (range, 60–82). No significant differences in the baseline characteristics of the two groups were observed, except in history of malignancy; a larger portion of elderly patients with ALL had a history of malignancy (p = 0.001). The composition of ALL subtypes and the frequencies of Ph+ status were not statistically significant between the two groups. The peripheral blood sample laboratory findings showed more severe anemia in younger adult patients with ALL than in the elderly patients (p = 0.023); of 26 elderly patients with ALL, abnormal karyotypes were found in 14 patients (53.8%) [38, 39].

All patients, with the exception of two elderly patients who received supportive care only, received induction chemotherapy. About half of the elderly patients (12 patients, 46.2%) received the VPDL regimen as an induction therapy. Five elderly patients (19.2%) were administered the VPD regimen, and one (3.8%) was administered the hyper-CVAD (cyclophosphamide 300 mg/m^2, D1–3; vincristine 2 mg D4,11; Adriamycin 50 mg/m^2, D4; dexamethasone 40 mg D1–4, D11–14) regimen. The overall CR rate was much higher in the younger adult patients than that in the elderly patients (94.1 vs. 57.7%, p < 0.001). Early mortality within 3 months from the start of induction chemotherapy was remarkably higher in the elderly patients (26.9% vs. 5.0%, p = 0.003).

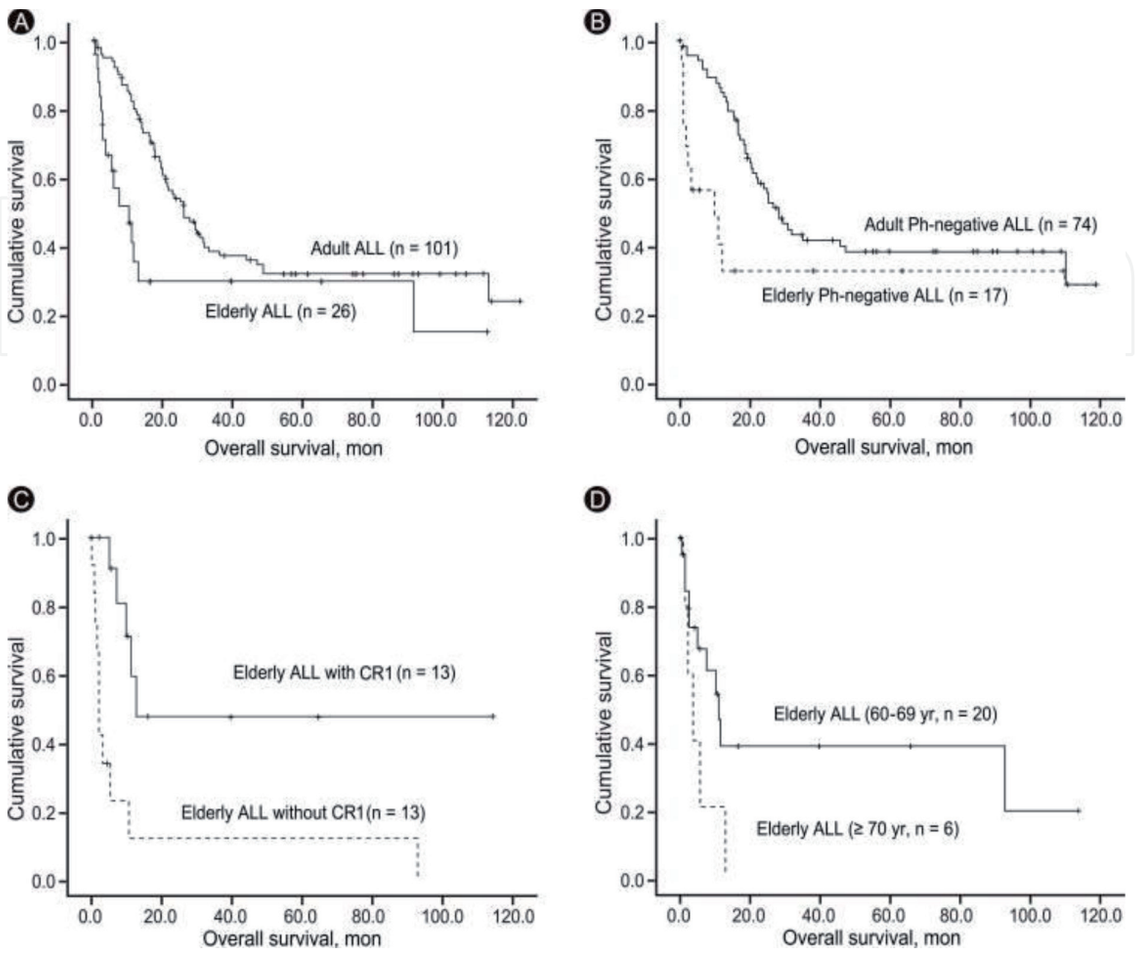
The median number of postremission consolidation therapy sessions was three (range, 1–5) in the elderly patients with ALL. The regimen in the elderly patients was vincristine and prednisolone in seven patients. Two patients received only imatinib due to severe comorbidities. One patient received the CALGB 9251 regimen, and the other patient received nonmyeloablative hematopoietic stem cell transplantation (HSCT) from a matched sibling donor. Of 15 elderly patients who achieved CR, only 11 received postremission therapy. The overall nondisease-related mortality rate in the elderly patients was higher than that in the younger adult patients.



Cumulative hazards of disease-related and nondisease-related mortality in younger adult patients (<60 years) with acute lymphoblastic leukemia (ALL) and in elderly patients (≥60 years) with ALL (p = 0.001 and 0.12, respectively).

The median OS of the younger patients was 26.3 months (95% confidence interval [CI], 19.6–33.0), whereas that of the elderly patients was 10.3 months (95% CI, 3.5–17.2) (p = 0.003). The survival difference according to age was not reproduced

in the subpopulation of patients with Ph-positive ALL (data not shown), but was consistently found in the patients with Ph-negative ALL.



A. Overall survival (OS) of elderly and younger adult patients with acute lymphoblastic leukemia (ALL): OS of elderly patients with ALL (≥60 year) was shorter than that of younger adult patients with ALL (<60 year) (median OS 10.3 vs. 26.3 months, respectively, $p = 0.003$).

B. OS of the elderly and younger adult patients with Philadelphia chromosome (Ph)-negative ALL: OS of the elderly patients with Ph-negative ALL (≥60 year) was shorter than that of adult patients with Ph-negative ALL (<60 year) (median OS, 10.3 vs. 29.2 months, respectively, $p = 0.01$).

C. OS according to complete remission in elderly patients with ALL: OS of elderly patients with complete remission was longer than that of elderly patients without complete remission (median OS, 13.1 vs. 2.6 months, $p = 0.001$).

D. OS according to age (60–69 vs. ≥70 years) in elderly patients with ALL: OS of elderly patients aged 70 years or more was not significantly different from that of the other elderly patients (median OS, 11.2 vs. 3.7 months, $p = 0.073$) [40, 41].

8. Survival analysis for elderly patients with ALL

Among the elderly patients, the patients who achieved CR1 (CR after the first induction chemotherapy) showed significantly longer survival compared with those

who did not achieve CR1 (median OS, 13.1 vs. 2.6 months; $p = 0.001$). Furthermore, CR1 was the only independent prognostic factor for OS in elderly patients with ALL ($p = 0.001$). Although the OS of elderly patients aged 60–69 tended to be longer than that of those aged 70 or over, the difference did not reach statistical significance (median OS, 11.2 vs. 3.7 months; $p = 0.073$).

In the survival analysis using the factors at the initial ALL diagnosis, the probable poor prognostic factors for CR were age ≥ 70 years (relative rate of remission [RR], 0.14; 95% CI, 0.013–1.45; $p = 0.098$) and leukocytosis (≥30,000/μL) (RR, 6.00; 95% CI, 0.93–38.63; $p = 0.059$). T-cell lineage and the presence of lymphadenopathy were significant factors in poor prognosis for OS in the univariate analysis (hazard ratio [HR], 3.11 and 3.14; 95% CI, 1.14–9.34, and 1.01–9.99; $p = 0.033$ and 0.041, respectively). T-cell lineage and Ph-positive status tended to increase the HR for leukemia free survival (LFS) (HR, 8.49 and 4.49; 95% CI, 0.53–135.82 and 0.8–25.21; $p = 0.069$ and 0.064, respectively).

Univariate analysis for complete remission, overall survival, and leukemia-free survival in elderly patients with ALL (≥60 year) (n = 26).

	Complete remission			Overall survival			Leukemia-free survival		
	RR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age ≥ 70	0.14	0.013-1.45	0.098	2.60	0.88-7.67	0.073	4.48	0.41-49.46	0.18
T-cell lineage	0.22	0.019-2.53	0.23	3.11	1.14-9.34	0.033	8.49	0.53-135.82	0.069
Ph(+)	3.38	0.52-21.73	0.20	1.11	0.40-3.12	0.84	4.49	0.8-25.21	0.064
Lymph adenopathy	0.21	0.018-2.33	0.20	3.14	1.01-9.99	0.041	4.48	0.41-49.46	0.18
Male	0.50	0.09-2.73	0.42	1.80	0.57-5.64	0.31	1.13	0.20-6.26	0.89
Fever	1.67	0.13-21.20	0.69	0.84	0.19-3.72	0.82	0.033	0.00-253.78	0.22
WBC ≥ 30,000/μL	6.00	0.93-38.63	0.059	0.50	0.17-1.46	0.19	0.99	0.17-5.98	0.99

ALL, acute lymphoblastic leukemia; RR, relative rate of remission; CI, confidence interval; HR, hazard ratio; Ph, Philadelphia chromosome; WBC, white blood cell.

The low response to chemotherapy in the elderly patients with ALL could be related to several factors. The first factor may be chemotherapy intensity. Intensified combination induction chemotherapy can result in an improvement in the CR proportion, and high-dose postremission methotrexate (MTX) or cytarabine therapy is effective for treating adult ALL. However, most elderly patients with ALL in our study could not receive the postremission therapy after the induction therapy with a standard or reduced dose and also could not be treated with intensified postremission regimens such as cyclophosphamide or MTX, though they received postremission therapy. The second factor may be drug-resistance mechanisms such as the presence of multidrug-resistance gene 1 and multidrug-resistance-related protein.

Although intensified induction chemotherapy was not introduced, and postremission therapy was not performed appropriately in most elderly patients with ALL, the survival benefit was definite in the patients who achieved CR. Our study did not show a statistical difference in nondisease-related mortality rates between the elderly and younger adult groups. However, the actual risk of nondisease-related mortality might be significantly higher in the elderly patients considering that only a few patients could receive highly toxic therapy such as HSCT, and our results indicated that about half (43.8%) of nondisease-related mortality was related to HSCT in the younger adult patients with ALL [40–43].

8.1 New treatment options in older patients with ALL

ALL blasts express a number of antigens, such as CD33, CD22, CD19, and CD52, which could be targets for antibody therapy. The majority of older patients suffer

from B-precursor ALL. In this subtype, approximately half of the patients show CD20 expression on their blast cells. In younger patients with $CD20^+$ ALL, the first promising data for the combination of chemotherapy and rituximab have been reported. Outcome of older patients could be hampered by a higher mortality due to infections in CR, which underlines the need for intensive supportive care for older patients throughout the entire treatment period.

A great majority of cases with ALL in elderly patient correspond to B-precursor lineage, one of the characteristics of this lineage is the expression of CD20 on its surface, which makes it susceptible to treatments focused on this marker, such as rituximab, this treatment approach has already shown to be highly effective in young patients, which could be transposed to the population over 65 years of age.

A promising new approach is the administration of a bispecific CD19 antibody, blinatumomab, which has the potential to engage cytotoxic T cells in patients for lysis of $CD19^+$ leukemia cells. In 19 patients with refractory disease, defined as hematologic remission with persistent MRD after intensive chemotherapy, the molecular remission rate was 84%. A number of older patients who were not able to receive an SCT remained in remission for more than 1 year. More recently, a CR rate of 68% was reported for relapsed ALL. All patients with CR also achieved a molecular CR. Treatment with the final dosing regimen was well tolerated, and a number of older patients experienced a benefit. The CD22 directed, calicheamicin-conjugated antibody inotuzumab induced 18% CRs and 39% marrow CRs in relapsed $CD22^+$ ALL. Toxicity appeared to be manageable, and the mortality of 4% within 4 weeks was moderate. Successful future use of antibody treatment will certainly depend on well-designed combination regimens with chemotherapy that aim to achieve long-term responses, particularly in older ALL patients.

In recent years, there have been advances and new therapeutic options in the management of ALL, one of the most promising is immunotherapy, specifically bispecific antibodies, the first of which useful information was disclosed was blinatumomab, this antibody that acts by binding to T lymphocytes, activating them and forcing them to destroy CD19 receptor expressing cells, such as blasts, already has multiple studies in various population groups that demonstrate their effectiveness against the disease, achieving significant response rates (84%) and negativization of the MRD. Another new specific antibody against the CD22 receptor, inotuzumab, has also been shown to be effective, at least in its initial studies, with a tolerable safety profile. The great advantage of these new treatments is that they do not confer the implicit risk in chemotherapy; however, there are no studies specifically in elderly patients.

Several other new drugs are of interest for optimizing treatment in older ALL patients. Although the number of older patients with T-ALL is low, the use of nelarabine is of interest after promising results and acceptable toxicity in relapsed T-ALL including older patients. Liposomal cytarabine for intrathecal application showed activity and tolerability in CNS relapse of ALL, although in combination with systemic neurotoxic regimens, severe toxicities may be observed. The use of liposomal cytarabine in prophylaxis of CNS relapse is of interest, particularly in older patients, since it allows reduction of the number of intrathecal injections and may induce fewer systemic toxicities compared to conventional intrathecal therapy.

Other drugs of current interest include nelarabine, indicated for use in cases of T-ALL. The prophylactic treatment to CNS has also had new protagonists in its field, liposomal cytarabine is one of these; this drug used for both prophylaxis and management of relapse to CNS has shown to be safe, although when combined with other neurotoxic agents, there is considerable toxicity. Despite this, safety is comparable to that presented by conventional cytarabine, with a higher rate of effectiveness.

Liposomal vincristine is another drug of interest, particularly in older patients. Results are still pending on the major question of whether liposomal encapsulation allows a higher dose intensity with lower risk of neurotoxicity. Bendamustine could be of interest, since it has shown limited toxicity and favorable results in older patients with B-cell lymphoma. New drugs with different mechanisms of action may, in the future, be used in combination with chemotherapy, such as proteasome inhibitors, histone-deacetylase inhibitors, hypomethylating agents, or targeted drugs such as Flt3 inhibitors or Jak2-inhibitors in defined subgroups of ALL. Currently, these compounds are either available in clinical trials or could be considered in individual patients with poor response to standard chemotherapy, including patients with molecular failure [12, 23, 43, 44].

Bendamustine and liposomal vincristine are new tools already known, the first one, a drug developed in the 1960s, has shown its effectiveness in various studies in the management of ALL and other lymphoproliferative disorders, with adequate safety in elderly patients. New mechanisms of action must be explored in order to give variety to the maneuvers against the disease. The study of new prognostic and risk markers that can be targeted by these drugs is crucial for their development. Currently, a large number of studies are underway in the world, both with new combinations of already known drugs and with novel molecules applicable to ALL [12, 23, 43, 44].

9. Conclusion

All older ALL patients need a comprehensive diagnostic classification, including, at least, immunophenotyping, molecular diagnostics, and setup of an assay for MRD evaluation. The identification of Ph+ ALL is crucial since, even in very old and frail patients, TKIs induce a high CR rate with reasonable durability. Furthermore, the biological characterization of older ALL patients needs to be improved. Biobanking for future scientific investigations within clinical trials should therefore be standard in older as it is in younger patients.

Altogether, in older as in younger patients, a pediatric-based induction strategy is recommendable in Ph− ALL. Dose reductions for anthracyclines are essential, and asparaginase during induction cannot be recommended outside of clinical trials. Dexamethasone appears to increase efficacy in younger patients, but prolonged use should be avoided. For fit older patients, consolidation chemotherapy may be intensified. Moderate-dose consolidation, including methotrexate, cytarabine, and reinduction therapy, appears to be feasible, and maintenance treatment is an essential treatment element.

In unfit older patients, a dose-reduced induction therapy is recommended with the aim of controlling and achieving a prolonged low-level disease. ALL-specific approaches should be considered, including vincristine, steroids, intrathecal therapy, and maintenance with mercaptopurine and methotrexate. Many physicians have more experience with older AML patients; however, there is no rationale for using AML regimens such as low-dose cytarabine or hydroxyurea in ALL.

When they are available, targeted drugs such as nelarabine, monoclonal antibodies, or other new drugs with potentially reduced or alternative toxicity should be added to treatment strategies in older patients, preferably in clinical trials. Since many of these compounds are used off-label, it may be useful to make the indication based on persistent MRD, which, in addition, offers a chance to evaluate effects immediately. Treatment options may change as soon as new drugs or strategies become available. With effective drugs for prolonged maintenance, it may be possible to further reduce intensity of induction therapy and avoid early mortality in unfit patients.

In Ph+ ALL, it is still not clear whether further reduced induction chemotherapy adds an effect to TKI therapy and which inhibitor is preferable. I favor a combination therapy. Moderate dose consolidation and maintenance should be offered. Patients should be considered as candidates for RIC SCT.

Whereas full-conditioning regimens before SCT are clearly not recommended, RIC SCT is an option in older patients. For indication, it will be crucial to define prognostic factors. Because persistence of MRD is one of the most important risk factors, MRD evaluation should take place in older patients to identify those who could benefit from experimental therapies or SCT. This also applies to Ph+ ALL regarding the option of changing the TKI.

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