Manejo actual de la Leucemia Linfoblástica Aguda

Management of Adult Acute Lymphoblastic Leukemia (ALL)

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Leucemias Agudas

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Introduction

Acute lymphoblastic leukemia (ALL) is a malignant disorder that originates from hemopoietic precursors, that can be of B-cell (80-85%) or T-cell (20-25%) derivation. It is likely that the acquisition of a series of genetic aberrations - some of which still unknown - leads to an impaired maturation, with an arrest in the differentiation process and an abnormal proliferation. As a consequence, the accumulation of leukemic cells occurs in both the bone marrow, where it suppresses the physiologic hemopoiesis, as well as in extra-medullary sites[1].

ALL is the most common neoplasm in childhood, with the highest peak of incidence in children with an age comprised between 2 and 5 years, whereas it is rather rare in adulthood. In fact, according to US-SEER, approximately 60.3% of ALL cases are diagnosed under the age of 20, 10.3% between 20 and 34, 5.9% between 35 and 44, 6.7% between 45 and 54, 6.1% between 55 and 64, 5.0% between 65 and 74, 4.0% between 75 and 84 and 1.7% in patients older than 85 years.

Among the potential contributors to ALL initiation, exposure to ionising radiations has been identified as a predisposing cause and an inherited predisposition has been proposed, at least in children. For the latter, in fact, by genome wide association studies it has been possible to identify some variants - i.e. *IKZF1*, *ARID5B*, *CEBPE*, *CDKN2A* and *PAX5, BMI1-PIP4K2A* and *GATA3* - that are associated with leukemia occurrence[2].

Beyond the different incidence of the disease and possibly the initiation causes, outcome varies profoundly between children and adults; in fact, to date, the majority of children (about 85%) can be considered curable, while the prognosis of adults is still much more unfavorable, with only 40-50%

of individuals being long-term free of their disease. Nevertheless, over the years an improvement in the survival likelihood has been observed also in adult patients, contributed by the therapeutic intensification of the current protocols and by the improvement of the overall clinical conditions of adult patients with ALL; furthermore, a significant improvement has been observed in specific subsets, such as Philadelphia (Ph/BCR-ABL1)+ ALL, Burkitt leukemia, T-lineage ALL and, more in general, in adolescents and young adults (AYA), which benefit from pediatric-based approaches and will be discussed separately.

For an optimal management of patients with ALL, some steps are of pivotal importance and they include a precise diagnostic work-up, a correct therapeutic strategy - particularly in specific subsets - and monitoring of minimal residual disease (MRD) for risk stratification and decision making in case of MRD persistence or reappearance.

This review will focus in particular on these topics.

Diagnosis

The starting point is a rapid, precise and accurate diagnostic work-up of patients of all ages. A morphological bone marrow assessment still represents the first step in the diagnostic work-up and for a differential diagnosis with acute myeloid leukemia (AML). Cytochemically, ALL blasts have negative peroxidase reactions and variable periodic acid-schiff (PAS) positivity. By definition, ALL blasts are negative for myeloperoxidase (MPO) and other myeloid cytochemical reactions. The classification of leukemic blasts has been recapitulated by the WHO classification[3].

Immunophenotyping, by means of multi-channel flow cytometry (MFC), has become pivotal for the diagnosis and subclassification of ALL, and is also useful for MRD detection. At diagnosis, it allows to discriminate between B-lineage and T-lineage ALL, not feasible by morphology, and permits to define the stage of differentiation of the leukemic cells. The European Group for the Immunological characterization of leukaemias (EGIL) has revised the general guidelines[4]. Among the novel subgroups that can be easily recognized by immunophenotyping, early-T precursor (ETP) ALL must be underlined[5].

Cytogenetics/molecular analyses[6, 7] are important for a precise work-up at diagnosis and are aimed at identifying major translocations/rearrangements, namely t(1;19)(q23;p13)/*E2A/PBX1*, t(12;21)(p13;q22)/*ETV6/RUNX1, MLL* rearrangements, translocations involving chromosome 8 *(c-myc* gene), such as t(8;14) (≈90% of cases), t(8;22) (≈10% of cases) and t(2;8) (very rarely observed), virtually present in 100% of cases of mature B-ALL with L3/Burkitt morphology and t(9;22)(q34;q11)/*BCR-ABL1*. The analysis of the latter rearrangement should be performed in the shortest possible time, for example during the steroid pre-phase used in many protocols, in order to optimize management of Ph+ ALL patients of all ages, given that these patients benefit by the administration of a tyrosine kinase inhibitor (TKI) (see dedicated paragraph) and should be included in the minimal diagnostic work-up requirement for all ALL patients, including the elderly.

More recently, the introduction of high-throughput techniques such as gene expression profiling (GEP), SNP array analysis, and, more recently, next generation sequencing (NGS) and whole exome sequencing (WES) has allowed to identify novel subgroups, such as the so-called BCR-ABL1-like cases. Furthermore, a set of lesions involving the JAK, RAS and PI3K pathways have been identified. It must be underlined, however, that at present these analyses should be considered investigational.

Principles of therapy

In general, the therapeutic backbone of ALL treatment is based on an induction phase based on 4-5 drugs (steroids, vincristine, antracyclines, asparaginase and cyclophosphamide) followed by early intensification/consolidation with high-dose methotrexate and cytarabine, and maintenance, with or without reinduction cycles, that can be prolonged for up to 24-36 months. Allogeneic stem cell transplantation (allo-SCT) in first complete remission (CR) should be reserved to patients with high risk factors, e.g. *MLL* rearrangements, t(9;22)(q34;q11)/*BCR/ABL1*+ cases and MRD persistence.

While this approach represents the general approach to ALL treatment, some subgroups have specific genetic features that translate into different therapeutic strategies. These are discussed below.

Specific subgroups

Ph+ ALL

Ph+ ALL represents the most frequent aberration in adult ALL: its incidence increases progressively with age (more than 50% in 6th decade of life), whereas it is extremely rare in pediatric cohorts (less than 5% in children younger than 10 years) [8]. Historically, Ph+ ALL was considered the ALL subgroup with the worse outcome, since the rate of complete hematologic remissions (CHR) with chemotherapy regimens was lower than that observed in other subsets and the 5-year event-free survival

(EFS) was below 20%[7]. The management and outcome of Ph+ ALL have dramatically changed since the introduction of TKIs, which induce higher remission rates and enable much better survival rates, also in elderly patients[9-16].

Currently, the inclusion of a TKI in the induction phase represents the gold standard management of Ph+ ALL patients, because it leads to much higher CHR rates and improved long-term outcome; it is now generally accepted that the use of a TKI has also the relevant advantage of increasing the likelihood of carrying out an allo-SCT in a greater number of patients compared to historical controls.

The use of imatinib as TKI, together with or following induction treatment, has led to a significant improvement in the management of Ph+ ALL patients, since remission rates outreached 90% in the majority of studies and improvements in disease-free survival (DFS) and overall survival (OS) rates were also recorded. A similar experience has been obtained also with the second generation inhibitor dasatinib, a more potent oral inhibitor of the BCR/ABL1, c-KIT and SRC kinase families, while few data are available with nilotinib. In spite of the clinical success achieved with these integrated approaches, it must be underlined that toxic deaths have been constantly recorded during induction in approximately 5% of cases.

The GIMEMA group[17-20] has, over the years, adopted an induction strategy based on the administration of a TKI, either imatinib or dasatinib or imatinib in rotation with nilotinib, plus steroids alone in induction, together with intrathecal central nervous system (CNS) prophylaxis without systemic chemotherapy. These regimens, utilized in adult and elderly populations (roughly 200 cases have been treated so far), have led to CHR rates in 96-100% of patients without toxic deaths in induction, thus indicating that this strategy is effective, feasible and safe (also in the elderly), and partly doable at home. Along a similar line of thought, the PETHEMA[21] and GRAAL[22] groups have both showed that a de-intensified treatment in induction is capable of inducing the same or better long-term outcomes as intensive treatments.

Remarkable results have been recently reported in an abstract form by the MDACC group[23] with a combination based on the pan-TKI ponatinib and the HyperCVAD regimen. The short-term results appear very promising: in fact, a CHR was achieved in all cases and a major molecular response in 75% of patients. With a median follow-up of 18 months, 31 patients are alive and 6 have died in CHR, 3 due to cardiac-related toxicities. The 1-year progression-free survival and OS rates are 96% and 86%.

Upon CHR achievement, consolidation/intensification treatment - which varies according to the different study groups but generally includes high-dose chemotherapy (particularly for younger patients) - is administered to further reduce and possibly eradicate MRD levels. Consolidation/intensification treatment should be performed in all cases with persistent MRD positivity, and even more importantly in individuals who are not suitable to receive an allo-SCT.

At present, allo-SCT still remains the only curative option for Ph+ ALL, mostly for younger adult patients. Recently, the EBMT[24] group has provided a comprehensive update on the role of allo-SCT in the TKI era in a cohort of 390 individuals. The following conclusions were reached: 1) as expected, TKI administration prior to transplant is associated to a significantly better OS both in univariate (47% vs 38% in the pre-TKI era) and multivariate analysis, and also correlates with a lower relapse rate in univariate (33% vs 50%) and multivariate analysis. 2) MRD at the time of transplant is not associated with differences in OS, leukemia-free survival (LFS), relapse rate and non-relapse mortality. It must, however, be underlined that MRD levels were not uniformly evaluated and this might represent a confounding factor. 3) The prophylactic administration of a TKI following allo-SCT improves LFS, OS and relapse rates. Given the toxic effects of this procedure, efforts are ongoing to identify patients who may possibly be spared this post-transplant TKI.

Autologous transplantation (auto-SCT) has recently been revisited in Ph+ ALL, mostly because TKI treatment allowed the achievement of sustained molecular responses and therefore better survival rates. Giebel et al[25] compared the outcome of patients stratified into three categories, according to the period in which the procedure was performed: 1996-2001 (no TKI treatment), 2002-2006 (TKI administered in sporadic cases), and 2007 onwards (TKI was administered in all patients) OS and LFS significantly increased among the three categories, being 16% and 11%, 48% and 39%, and 57% and 52%, respectively. Similar results were recently published by Chalandon and colleagues, who showed comparable results between allo- and auto-SCT[22].

An emerging issue is represented by the presence of mutations, with a predominance of P-loop and T315I mutations[26], the latter being insensitive to most TKIs with the exception of ponatinib. Another clinical challenge is represented by the occurrence

of the so-called compound mutations[27], defined as the presence of two or more mutations in the same molecule. For such cases, the use of alternative approaches is urgently required.

Burkitt leukemia

Burkitt leukemia, characterized by a peculiar morphology and immunophenotype, as well by rearrangements involving the *c-myc* gene, can be considered as a therapeutic success in hematology. In fact, the prognosis of patients with a diagnosis of Burkitt leukemia (L3 in the old FAB classification) has largely improved with the use of short-term, dose-intensive treatment programs. CR rates now exceed 80%, with 2-year DFS rates of 60% to 80%. Relapses, when they occur, are usually observed within the first year of remission. Intensive early prophylactic intrathecal therapy, together with high doses of cytarabine and methotrexate, reduces the CNS relapse rate. The addition of rituximab to chemotherapy has further improved the cure rates of this subgroup[28, 29].

BCR/ABL1-like ALL

The BCR/ABL1-like subgroup, identified by means of GEP, represents a novel subgroup that can be detected in both pediatric and adult cohorts[30, 31]: this entity seems to be particularly frequent in the AYA group, where it reaches 25%-30%, as opposed to ≈10% of children. Several genetic lesions have been unraveled: in fact, these patients often harbor deletions of the transcription factor *IKZF1*, deregulation of *CRLF2* - sustained either *by IGH-CRLF2* rearrangements or by an interstitial deletion of the pseudoautosomal region of sexual chromosomes (*P2RY8-CRLF2)* - and a large set of lesions that involve several tyrosine kinases. Among the most frequent, it is worth mentioning *NUP214-ABL1*, in-frame fusions of *EBF1-PDGFRB*, *BCR-JAK2*, *STRN3-JAK2* and the cryptic *IGH-EPOR* rearrangements, *ABL1*, *ABL2* and *CSF1R* rearrangements, and *JAK1/2* mutations[30, 32]. While at present much is known about the genetic lesions associated with this subset, it must also be reminded that, so far, the recognition of these cases relies mostly on GEP analysis, not routinely performed in most centers, and that there is not a recurrent common lesion underlying the signature identified. Current efforts are ongoing in an attempt to easily and rapidly identify these cases.

From a clinical standpoint, the recognition of this subgroup is crucial, for two main reasons: 1) prognosis in these patients is usually poor, although it has been recently shown that in childhood cases MRD-based risk-directed therapy[33], including transplant procedures, might overcome the unfavorable outcome; 2) given the plethora of alterations affecting several tyrosine kinases and their downstream targets, it is plausible that the use of TKIs and/or mTOR inhibitors might be of benefit in these patients. In fact, while few reports are available on the clinical management of BCR/ABL1-like ALL, it has been shown that BCR/ABL1-like refractory patients treated with TKIs may achieve rapid and sustained responses[32]. Similar findings have been reported in two cases harboring *EBF1-PDGFRB* or *ATF7IP/PDGFRB* rearrangement treated with imatinib or dasatinib[34, 35], so that TKI integration could be a suitable approach. The right timing for TKI needs to be further investigated, possibly in prospective clinical trials.

T-lineage ALL

The outcome of patients with T-ALL is nowadays similar to that of patients with B-ALL, thanks to the use of more intensive treatments. Furthermore, while in the past the spectrum of genetic lesions was limited to rearrangements involving the T-cell receptor genes (TCR), knowledge in T-ALL has greatly increased over the years[36]. Indeed, a large set of mutations has been identified in T-ALL by sequencing, re-sequencing and NGS, and include *NOTCH1*, *FBW7*, *BCL11B*, *JAK1*, *PTPN2*, *IL7R* and *PHF6*. Some of these lesions are of prognostic significance: in fact, *NOTCH1* and/or *FBW7* mutations, which occur in more than 60% and about 20% of cases, respectively, are usually associated with a more favorable outcome. In light of this, a prognostic model has been recently proposed by the GRAAL group[37] that defined as low-risk patients those harboring *NOTCH1* and *FBW7* mutations, and as high risk those without these mutations or harboring lesions involving *RAS/PTEN*. Moreover, although with some contrasting results, *JAK1* mutations[38-40], which increase JAK activity and alter proliferation and survival, have been associated with chemotherapy refractoriness and should be considered as poor prognostic markers. Finally, *JAK3* mutations have been identified[41], but their prognostic role needs to be better investigated.

A specific subgroup identified within T-ALL is represented by ETP-ALL [5]. As mentioned earlier, this subset can be easily recognized by flow cytometry since it is characterized by distinct cell surface features: absence of CD1a, weak CD5 expression and the expression of one or more myeloid or stem cell-associated markers. Several genomic lesions have been identified: beyond *NOTCH1*, mutations

in *DNMT3A*, *FLT3*, *IDH1*, *IDH2* and *ETV6* have been reported. Interestingly, *FLT3* can be detected in up to 35% of cases, thus implying the possibility of novel therapeutic strategies[42]. Furthermore, mutations occurring in genes regulating cytokine receptors and RAS signaling (67%), inactivating lesions disrupting hematopoietic development (58%) and histone-modifying genes (48%) have been reported, suggesting that ETP-ALL shares a similar genomic background with AML. Clinically, this subgroup was initially defined as a poor prognosis subset; however, the prompt recognition of ETP cases is improving their outcome: allo-SCT in first CR should be considered the optimal choice for these patients. Finally, the presence of AML-related features prompts to investigate the use of myeloid-directed therapies.

Adolescents and young adults (AYA)

Although survival rates are now in the order of 85% for childhood ALL, older AYAs have a much poorer prognosis. Factors accounting for the differences in outcome include heterogeneity in disease biology, host factors (both physiologic and psychosocial) and, importantly, the therapeutic approach and the referral center, being either a pediatric or an adult care hospital. The definition of this age group is somehow confusing, although the National Cancer Institute has defined the AYA cancer population as being between the ages of 15 and 39 years[43].

Among the biologic factors observed in AYA, a T-lineage phenotype appears to be more common in AYA, as well as an ETP phenotype. Good-risk cytogenetic aberrations, such as *ETV6/RUNX1* rearrangements and hyperdiploidy tend to disappear with age progression, whereas the BCR/ABL1 rearrangement and the BCR/ABL1-like features tend to increase; as mentioned above, the latter seems to prevail in the AYA group.

With regard to host factors, several features are responsible for increased treatment toxicity, including differences in the metabolism of chemotherapeutic agents, depleted marrow reserve and increased extramedullary toxicity, overall resulting in an increased frequency of life-threatening infections, organ failure, treatment delays and dose reductions in planned chemotherapy compared to childhood ALL. It has been hypothesized that treatment intensification and introduction of pediatric-oriented regimens in AYA might improve the outcome of these patients. Indeed, several comparative retrospective studies have shown a clear advantage in treating AYA with these approaches, leading to a 5- to 6-year event-free survival (EFS) that overcomes 60% (44-48), as opposed to 30-50% with adult-based protocols (with few exceptions[49]). These differences are likely to be ascribed to the use of higher doses of drugs and introduction of asparaginase.

Currently, several prospective clinical trials worldwide are using pediatric-inspired[50-52] or unmodified pediatric protocols[53] for AYA with extremely variable age limits. While these trials confirm the overall efficacy of this strategy, it must be noted that in older AYA patients the percentage of deaths in CR and chemotherapy-related deaths may be high, thus indicating that these regimens should possibly be administered up to the age of 40.

Minimal residual disease

Monitoring of MRD has become routine clinical practice in the frontline treatment of virtually all childhood ALL and in many adult ALL patients. MRD has proven to be the strongest prognostic factor, allowing for risk group assignment into different treatment arms and has led to significant treatment reduction or intensification[54].

The MRD techniques need to be sensitive ($\leq 10^{-4}$), broadly applicable, accurate, reliable, fast and affordable. The most common techniques are represented by flow cytometry, polymerase chain reaction (PCR) analysis of rearranged immunoglobulin (Ig) and TCR (allele-specific oligonucleotide [ASO]-PCR) genes and RQ-RT-PCR methods for fusion genes, if present. All methods have some disadvantages: flow cytometry is less sensitive than ASO-PCR and RQ-RT-PCR, mostly when 4- and 6-colors are used; ASO-PCR represents the most reliable approach, but it is time-consuming since it is based on the identification of at least one patient-specific target, not feasible in a proportion of cases (roughly 10%) and requires a strong expertise; finally, RQ-RT-PCR is highly sensitive (10^{-4}-10^{-6}) and relatively easy to perform; however, full standardization of all steps and international QA systems are not yet available.

At present, intensive research is ongoing[55] to validate novel tools to improve MRD monitoring, such as NGS and digital droplet PCR (ddPCR)[56].While the time points for MRD evaluation can slightly differ between childhood and adult ALL, MRD monitoring, also early during induction in childhood[56], at the end of this phase, consolidation in pediatric and adult cohorts[57], is an important prognostic factor, and can drive therapeutic intensification

The time points for MRD evaluation adopted in pediatric and adult protocols differ slightly[57]: nonetheless, MRD is performed during induction (also at early phases in children, i.e. day +15 [58]) and at the

end of induction for treatment intensification. MRD evaluation during consolidation and follow-up is also crucial, because MRD persistence or reappearance is associated with hematologic relapse and, again, can drive therapeutic decisions, also in light of the novel compounds available (see below).

Novel therapeutic approaches: monoclonal antibodies

Despite the improvements documented over the years, a large fraction of adult patients still relapses, and in these cases achievement of a durable second CR is unlikely. One of the most exciting developments under investigation in relapsed/refractory (R/R) ALL are monoclonal antibodies, particularly blinatumomab, targeting CD19 and CD3, and inotuzumab ozogamicin, targeting CD22. These compounds can induce second CR and represent a potential bridge to allo-SCT.

Blinatumomab was first assessed in patients with MRD+ ALL[59]. Adult patients with molecularly refractory disease or with a molecular relapse were eligible. Twenty-one patients were enrolled and received a dose of 15 μg/m^2 for 4 weeks per cycle as continuous infusion followed by a 2-weeks period of wash-out: MRD negativity was achieved in 16 (80%) cases and 8 of them proceeded to an allo-SCT. Subsequently, its role was investigated in patients with R/R ALL at a higher dose (28 μg/m^2). In the pivotal trial[60], the overall response rate (ORR, CR or CR with incomplete count recovery) within 2 cycles of therapy was 69%. The estimated median survival was 9.8 months. In a confirmatory, open-label, single-arm, multicenter phase 2 study in 189 patients with R/R disease, the ORR was 43%, with 80% of the responses occurring within the first cycle. The median response duration and the OS were 9 and 6 months, respectively[61]. The toxicity profile of blinatumomab is acceptable and consists of fever, chills, and hypogammaglobulinemia, related to a cytokine release syndrome (CRS) that occurs shortly after the start of therapy. Tremor, headache, other mental status changes (eg, confusion), and, rarely, seizures have been reported: adequate prophylaxis is capable of overcoming these effects.

The immunoconjugate directed at CD22, inotuzumab ozogamicin, is linked to calicheamicin, that induces double-strand DNA breaks. This compound was initially used at a starting dose of 1.3 mg/m^2 every 3 to 4 weeks for the first 3 patients and later escalated at 1.8 mg/m^2 in a single-institution phase 2 study in patients with R/R ALL[62]; in the 49 patients treated, the ORR was 57% and the median survival was 5.1 months. Nearly half of the patients treated with inotuzumab were able to proceed to an allo-SCT. Survival was similar whether patients underwent a subsequent allo-SCT or not. Transient fever and hypotension were the two most frequent non-hematologic adverse events, and they typically occurred shortly after inotuzumab infusion. Liver function abnormalities were also observed, but they tended to be reversible, whereas serious toxicity in the transplant group included the development of veno-occlusive disease (VOD) in about 20% patients. To optimize the benefit/risk of inotuzumab, the dosing was modified: 0.8 mg/m^2 on day 1 and at 0.5 mg/m^2 on days 8 and 15 every 3 to 4 weeks. While achieving comparable ORR (59%) and a median survival of 9.5 months, this regimen proved less toxic[63]. A randomized trial comparing inotuzumab with a physician's choice of chemotherapy in patients with ALL in first and second salvage has completed accrual.

Concluding remarks

The advancements in the management of adult ALL are encouraging and are mainly dependent on the more refined recognition of specific subgroups, for which treatment is different/tailored, on the incorporation of MRD monitoring for a further personalization of treatment and on the use of targeted approaches, where feasible. The administration of monoclonal antibodies in front-line strategies and the progressive broadening of targeted treatment strategies is likely to further improve the results obtained so far, and lead to a scenario more similar to that observed in pediatric patients.

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