CURRENT MANAGEMENT OF ADULT ACUTE LYMPHOBLASTIC LEUKAEMIA: EMERGING INSIGHTS AND OUTSTANDING QUESTIONS

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ABSTRACT

Less than 50% of patients with adult acute lymphoblastic leukaemia (ALL) experience long-term survival and for those adults >60 years old, long-term survival rates are only 10%. However, significant advances have been reported over the last decade. Both the efficacy of chemotherapy and the safety of transplants have improved. Improved outcomes have been seen in younger adults treated with paediatric-inspired chemotherapy regimens. Minimal residual disease has been identified as an independent predictor of relapse risk and is currently widely used for risk-adapted treatment. Newly developed targeted therapies have been developed to improve treatment outcomes. Tyrosine kinase inhibitors (TKI) have become an integral part of front-line therapy for Philadelphia (Ph) chromosome positive ALL. Ph-positive ALL serves as the first example of truly targeted treatment, although the choice of the most effective TKI is not yet settled. The last few years have also seen a surge in immune therapies for B cell lineage ALL. The success of the anti-CD20 monoclonal antibody rituximab provided proof-of-principle for exploiting the immune system therapeutically. Novel immune therapies recruit (bispecific T cell engager) or modify (chimeric antigen receptor T cells) the patient’s own T cells to fight leukaemic cells. These new approaches led us to predict that ALL therapy might be based heavily on non-chemotherapeutic approaches in the near future. The role of allogeneic stem cell transplantation is also increasingly called into question. Herein, we review the background and development of these distinct treatments, and assess the current clinical knowledge of their efficacy and safety.

Keywords: Acute lymphoblastic leukaemia (ALL), treatment, targeted therapy, allogeneic stem cell transplantation (SCT), prognosis.

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is a malignant neoplasm of the lymphocyte precursor cells. ALL is characterised by aberrations in proliferation and differentiation of lymphoblasts, leading to failure of normal immune response and decreased haematopoiesis. It represents a heterogeneous group with distinct morphologic, cytogenetic, and molecular groupings. It is a clonal disease that can be separated by immunophenotyping into a B lineage ALL group (about 75%) and a T cell lineage ALL group (about 25%) and their subtypes according to the stage of maturation/differentiation. Standard cytogenetics, fluorescence in situ hybridisation, and reverse transcriptase polymerase chain reaction (RT-PCR) allow the detection of chromosomal translocations and the corresponding gene rearrangement. The identification of these rearrangements has provided critical insights into leukaemogenesis and is currently central to risk stratification. Gene expression profiling, novel molecular techniques, and next-generation sequencing can also recognise newly defined ALL entities.

ALL remains a major therapeutic challenge in adults. In this review, we cover the clinical and biological characteristics, pathophysiology, and therapy for ALL. The evidence for minimal residual disease (MRD) is discussed as well as novel...
molecular targets and newly developed therapies, such as new immunotherapeutic approaches.

**TREATMENT PRINCIPLES**

Most therapeutic advances in adult ALL have arisen from adaptation of ALL treatment in children. Historically, induction therapy for adult ALL has been built around a ‘backbone’ of vincristine and prednisone. Standard induction regimens can be labelled as four-drug or five-drug (vincristine, prednisone, anthracycline, cyclophosphamide, and L-asparaginase) regimens. Modifications in the chemotherapeutic schedule could concern the type and timing of corticosteroids, the addition of other drugs during induction, intensification of anthracycline dose, or introduction of high-dose cytarabine to provide efficient prophylaxis of central nervous system (CNS) relapse. However, these approaches do not appear to be superior to conventional treatment, and it remains uncertain as to which subgroups would benefit in terms of leukaemia-free survival (LFS) following such modifications.

The goal of induction chemotherapy is to achieve a morphologic clinical remission (CR), or better still, a complete molecular response. With current regimens, the CR rate reaches 80–90%. Long-term survival reaches 80–90% with chemotherapy only in Burkitt-like ALL, 60–75% with chemotherapy alone in standard-risk B cell lineage ALL, >50% with chemotherapy and allogeneic stem cell transplantation (SCT) in high-risk Philadelphia (Ph)-negative B cell lineage ALL, and 50–60% in Ph-positive ALL. In T cell lineage ALL, long-term survival is observed in 60–70% with chemotherapy alone in the thymic subtype, in about 50% with chemotherapy and allogeneic SCT in the mature T subtype, and in 30–40% with chemotherapy and allogeneic SCT in the early T precursor ALL subtype. Over the past decades, survival in ALL has improved in all age groups except for those $>$60 years old. Using elderly-specific protocols with less intensive therapy, a CR rate of about 71% has been demonstrated. Early death rate was 15% and the median overall survival (OS) was 33 months.

Salvage chemotherapy results are comparatively poor in the setting of refractory/relapsed ALL. Only 30–40% of adults achieve a second CR and 10–20% in further salvages. The median OS ranges from 4.5–8.4 months and 5-year survival rates are just 7–10%. At this stage, only allogeneic SCT offers a chance of long-term survival, however few patients can be bridged to this treatment.

**RISK STRATIFICATION**

**Standard Prognostic Factors**

Standard prognostic factors (age, white blood cell count, immunophenotyping, cytogenetics, and genetic aberrations) are identified at the time of diagnosis. Patients without any risk factors are considered as standard-risk patients and are treated with chemotherapy courses only. Patients displaying one or more risk factors are classified as high-risk patients and are candidates for allogeneic SCT in first CR. Treatment decision making will soon be refined in accordance to risk stratification based on genetics at diagnosis and MRD after induction therapy.

**Genetics of Acute Lymphoblastic Leukaemia**

Multiclonoality at diagnosis is common in ALL. The ALL genome is not static but evolves over time. The advent of microarrays and sequencing has demonstrated acquisition of new deletions and mutations and the loss of diagnosis-specific lesions at the time of relapse, but with preservation of key alterations. In the majority of cases, diagnosis and relapse clones arise from a common pre-leukaemic clone that has acquired genetic alterations required to established frank leukaemia. Many relapse-acquired lesions are enriched in specific pathways, including B cell development (IKZF1), tumour suppression (TP53), RAS signalling, chromatin modification (CREBBP, SETD2), and drug metabolism (NT5C2). Several alterations are known to confer resistance to specific chemotherapy agents and glucocorticoids. Initial therapy eradicates all subclones apart from those that survive to propagate relapse and acquire additional mutations that facilitate resistance to therapy. Recent studies have implicated epigenetic deregulation in leukaemogenesis and treatment failure in ALL. This involves mutations in genes that regulate the epigenome. These findings are of clinical relevance since the introduction of drugs that target histone readers (bromodomain inhibitors) and histone modifiers (histone demethylase and histone deacetylase inhibitors).

Multiple susceptibility loci associated with ALL risk have been recently identified. The most reproducible associations have been in genes that are also targets of somatic genetic alteration in ALL: IKZF1, ARID5B, CEBPE, and CDKN2A.
Minimal Residual Disease

MRD is the detection of residual leukaemic cells detectable as leukaemia-specific aberrant immunophenotypes by flow cytometry, leukaemia-specific rearranged immunoglobulin, or T cell receptor sequences by quantitative RT-PCR, or detection of fusion genes associated with chromosomal abnormalities. The detection limit is $10^{-3}$–$10^{-5}$. Measurement of MRD has significantly improved risk stratification and helped guide the intensification of therapy. MRD overrides all of the pre-therapeutic risk factors and is currently regarded as the most important prognostic factor for survival and a major component of a personalised treatment algorithm. MRD levels have been evaluated at various early time-points using either flow cytometry or immunoglobulin/T cell receptor gene amplification. For example in a French study, MRD was studied 6 weeks (MRD1) and 12 weeks (MRD2) after initiation of induction. MRD1 and MRD2 levels were strongly correlated. Patients with molecular response after induction chemotherapy had a significantly better outcome than those with a persistently positive MRD. MRD1 response allowed researchers to significantly discriminate high-risk versus standard-risk patients amongst those defined by their early morphological response. Therefore, patients achieving molecular remission are now considered as standard-risk patients, while those with a positive MRD are defined as high-risk patients. Persistence of a positive MRD after induction is an indication for allogeneic SCT in first morphological remission. Patients achieving MRD negativity after induction will only receive consolidation and maintenance chemotherapy. Of these patients, 20–30% will relapse because of loss of sensitivity, evolution of leukaemic subclones, or extramedullary localisation of the disease.

PAEDIATRIC-INSPIRED THERAPIES

Lessons have been drawn from the management of ALL in adolescents and young adults; studies in this patient subgroup have demonstrated improved survival for patients treated with paediatric rather than adult protocols. Reasons explaining this difference include differences in protocol designs with higher doses of drugs, early and more frequent CNS prophylaxis, and dexamethasone instead of prednisone; biological differences; different practice patterns; and social factors such as support systems and compliance.

Paediatric treatment protocols have thus been applied to adult patients, providing increased drug intensity at several stages of treatment including higher cumulative doses of corticosteroids, vincristine, and L-asparaginase. L-asparaginase is an integral component of therapy for ALL. The ability to identify patients with inadequate asparaginase activity is of great value in clinical decision making and has the potential to improve clinical outcomes. Serum asparaginase activity levels are the best and most reliable indicators of asparaginase activity. Trough asparaginase activity levels $\geq 0.1$ IU/mL appears to be a safe target to ensure therapeutic benefit. Screening for silent inactivation (development of asparaginase antibodies and asparaginase inactivity without the development of overt or recognised allergy symptoms) should be considered in all patients undergoing therapy for ALL with asparaginase. Survival rates at 5 years ranged from 67–78%, and compared favourably to rates between 34% and 41% observed with the former protocols. These emerging data showing substantially improved outcomes for younger adults question the role of allogeneic SCT in the upfront setting.

STEM CELL TRANSPLANTATION

Place of Transplantation in Acute Lymphoblastic Leukaemia

Allogeneic SCT in the first CR remains the standard of care for adults with high-risk ALL. In a recent meta-analysis, the 5-year OS was 49.9% for patients with a donor versus 42.7% for those without. However, graft-related toxicity after myeloablative conditioning remains an important issue and consideration should be given to the use of less intensive conditioning regimens. The 6-month and 2-year non-relapse mortality was 7.3% and 35.8% versus 2.0% and 13.6% in high-risk patients with donor and patients with no donor, respectively. In standard-risk patients, the 6-month and 2-year non-relapse mortality was 3.4% and 19.4% versus 1.2% and 6.9%, respectively. It is well established that relapse probability is higher in patients with no acute graft-versus-host disease (GvHD) as compared with patients with Grade I–III acute GvHD.

Reduced-Intensity Conditioning in Acute Lymphoblastic Leukaemia

Allogeneic SCT after reduced-intensity conditioning have been shown to be feasible in adult ALL.
Results appeared significantly better when performed in first CR as compared with second or further CR. No differences were found in terms of LFS when compared with allogeneic SCT after myeloablative conditioning.\textsuperscript{21,22} Allogeneic SCT after reduced-intensity conditioning with cord blood showed a 2-year OS of 50%, a 2-year non-relapse mortality of 27%, and a 2-year relapse rate of 36%.\textsuperscript{23}

**Haploidentical and Cord Blood Transplantations**

Allogeneic SCT from haploidentical donors has rapidly developed over the past few years.\textsuperscript{24} A higher probability of finding a suitable haploidentical donor has been demonstrated as compared with suitable umbilical cord blood. The other advantages are a shorter time-to-transplant and a lower cost.\textsuperscript{25} A large comparative study between unrelated cord blood and unmanipulated haploidentical SCT suggested that results are likely comparable, indicating that both transplant strategies are suitable for patients lacking a human leukocyte antigen (HLA) matched donor or when transplantation cannot be delayed.\textsuperscript{26} However, a lower treatment-related mortality was observed after haploidentical SCT (10% versus 23%), while relapse rate was identical (about 30%).

**TARGETED THERAPIES AND IMMUNOTHERAPY**

Monoclonal antibodies represent a new approach for the treatment of B cell lineage ALL.\textsuperscript{27} B lineage blast cells express a variety of specific antigens, such as CD19, CD20, and CD22. Unconjugated monoclonal antibodies have demonstrated efficacy in ALL. Anti-CD20 monoclonal antibody rituximab has improved the outcome of patients with Burkitt leukaemia/lymphoma.\textsuperscript{28,29} With repeated short cycles of intensive chemotherapy combined with rituximab, the 5-year OS of these patients increased from 60% to >80%.\textsuperscript{29} In precursor B ALL, Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, [also known by its trade name, Adriamycin\textsuperscript{\textregistered}], and dexamethasone) plus rituximab gave results significantly better than those observed with chemotherapy alone.\textsuperscript{30} These findings were confirmed by a German group\textsuperscript{31} and more recently by the randomised study from a French group showing a significant advantage with chemotherapy combined with rituximab with a 2-year OS of 71% versus 52% and a 2-year event-free survival (EFS) of 65% versus 52%.\textsuperscript{32} Adding rituximab to standard chemotherapy should therefore be the standard of care for these patients, although optimal dose schedule remains to be determined. Combination of chemotherapy with other anti-CD20 agents has also been tested. Ofatumumab combined with Hyper-CVAD showed 97% of CR and 67% of MRD-negativity after induction and a 2-year OS of 87%.\textsuperscript{33} Monoclonal antibodies directed against CD22, such as inotuzumab ozogamicin or epratuzumab are being evaluated as potential therapeutic agents for ALL. Inotuzumab ozogamicin, which links an anti-CD22 antibody to the chemotherapeutic agent, calicheamicin, showed a CR rate of 66% in relapsed/refractory ALL patients. Among remitters, 78% achieved a complete molecular response.\textsuperscript{34,35} In a Phase III study comparing inotuzumab to standard chemotherapy, complete response was obtained in 81% versus 33%, respectively.\textsuperscript{36} MRD-negativity in remitters was observed in 78% of cases versus 28%. In the mini-Hyper-CVAD-inotuzumab ± rituximab, the overall response rate was 97% with MRD-negativity in 100% of cases and the 2-year OS was 64%.\textsuperscript{37} Venous occlusive disease did not exceed 10%. An even more sophisticated antibody design is that of blinatumomab, a bispecific T cell engaging (BiTE\textsuperscript{\textregistered}) antibody, which directly recruits effector T cells to augment the anti-leukaemic effect. Blinatumomab contains the variable domains of a CD19 antibody and a CD3 antibody, which are joined by a non-immunogenic linker. On binding to CD19, cytotoxic T cells become activated and induce cell death via the pore-forming perforin system. In MRD-positive ALL, blinatumomab facilitated a switch to MRD-negativity in 80% of cases.\textsuperscript{38} In adult patients with refractory/refractory ALL, the response rate was 43% and the MRD response rate in remitters was 82%.\textsuperscript{39} The most frequently reported adverse events were Grade 3/4 reversible neurological events (17–19%).\textsuperscript{38,40} Monoclonal antibody development could however, be challenged by the novel approach based on chimeric antigen receptor (CAR) T cells targeting CD19, which has already been tested with encouraging first results.\textsuperscript{31} In relapsed/refractory patients, a response was obtained in 93% of cases, and the 1-year relapse-free survival was 55%.\textsuperscript{42} Immune toxicity after infusion correlates with disease burden. Treatment may consist of short courses of steroids and interleukin-6R antagonism via tocilizumab.\textsuperscript{43} A maximum tolerated dose (1x10\textsuperscript{6}/kg) was defined beyond which toxicity was frequently unacceptable.\textsuperscript{44} MRD-
negativity was reached in 50–83% of cases and a large proportion of patients went on to receive allogeneic SCT after CAR T cells.\textsuperscript{44,45} CAR T cells targeting CD22 or CD19/CD22 are under investigation.

**SPECIFIC SUBTYPES**

**T Cell Lineage Acute Lymphoblastic Leukaemia**

Genetic and epigenetic reprogramming events, which transform T cell precursors into malignant T-ALL lymphoblasts, have been extensively characterised over the past decade. T lineage ALL are distributed into different subtypes according to maturation stage: thymic (56%), early-T (23%), and mature-T (21%). A correlation has been reported between maturation stage and outcome with the best outcome for thymic T cell ALL (OS: 60–70%) compared with early (33%) and mature-T phenotypes (22%).\textsuperscript{46,47} T cell lineage ALL is caused by an accumulation of more than 10 genomic lesions.\textsuperscript{48} T-ALL leukaemic cells commonly have rearrangements which dysregulate oncogenes, including \textit{HOX11}, \textit{HOX11L2}, \textit{LYL1}, \textit{TAL1}, and \textit{MLL} genes.\textsuperscript{49} T-ALL exhibits a very high frequency of homozygous deletion of \textit{CDKN2A}/\textit{CDKN2B} and activating mutations of \textit{NOTCH1}. Genome-wide analyses have also identified deletions dysregulating \textit{LMO2}, amplification of \textit{MYB}, amplification associated with the \textit{NUP214-ABL1} rearrangement, fusion of \textit{SET} to \textit{NUP214}, and deletion and mutation of \textit{BCL11B}, \textit{FBXW7}, \textit{PHF6}, \textit{PTEN}, \textit{PTPN2}, and \textit{WT1}. Additional genetic defects are shared among the different genetic subclasses and activate oncogenic signalling cascades. The \textit{IL7R}/\textit{JAK1}/3-\textit{STAT5} axis is an important oncogenic pathway in T cell ALL which represents about 28% of mutant cases.\textsuperscript{50} There is a strong association between \textit{JAK1}/\textit{JAK3}/\textit{IL7R} and epigenetic mutations. \textit{IL7R} mutations result in ligand-independent receptor activation.\textsuperscript{51} Two types of \textit{JAK3} mutations are observed in T-ALL: \textit{JAK3} mutants that signal through \textit{JAK1} and \textit{JAK3} mutants that are \textit{JAK1} independent. The former are sensitive to \textit{JAK1} inhibition, such as tofacitinib or ruxolitinib.

In an attempt to start integrating molecular findings into the clinic, a French group has implemented a \textit{NOTCH1}/\textit{FBXW7}/\textit{RAS}/\textit{PTEN}-based risk classification, in which patients with mutated \textit{NOTCH1} or \textit{FBXW7} who present with a wild-type \textit{RAS} and \textit{PTEN} are considered low-risk, whereas all other adult T-ALL are classified as high-risk.\textsuperscript{52} Additional inclusion of poor prognostic genetic markers, such as \textit{DNMT3A}, \textit{IDH1}, and \textit{IDH2}, should be considered to further improve this risk stratification approach.

Recent studies have characterised early T cell precursor (ETP) ALL that lacks expression of several T cell markers and exhibits aberrant expression of myeloid stem cell markers.\textsuperscript{53} Recurring mutations have been described in various pathways: haematopoietic development, RAS and cytokine receptor signalling, and chromatin-modifying genes. Consecutively, ETP ALL belongs to the group of neoplasms that arise in progenitors that retain multilineage potential and possibly biphenotypic and bilineal ALL. The involvement of JAK-STAT and PRC2 pathways in this subtype of ALL suggests that JAK inhibition and/or chromatin-modifying agents may be therapeutically useful in ETP ALL.

Leukaemia patients with T lineage ALL are still treated by high-dose multiagent chemotherapy, potentially followed by allogeneic SCT. With regard to paediatric regimens, clinical studies have examined the dose intensification of non-myelosuppressive drugs. The use of dexamethasone, a higher total dose of methotrexate, or a higher total dose of L-asparaginase have been shown to improve outcomes of adult patients with T-lineage ALL.\textsuperscript{54} However, about 40% of these patients relapse, wing to acquired therapy resistance, and have a poor prognosis with high mortality rates. Following a better understanding of T cell pathology, several new therapeutic options are forthcoming, including the purine analogue nelarabine\textsuperscript{55} and the purine nucleoside phosphorylase forodesine.\textsuperscript{56}

Gamma-secretase, which participates in the release of the \textit{NOTCH1} intracellular domain before it translocates to the nucleus, is a potential therapeutic target. Gamma-secretase inhibitors were shown to enhance the apoptotic effect induced by chemotherapeutic agents\textsuperscript{57} or dexamethasone.\textsuperscript{58} Alternative strategies include specific NOTCH1-inhibitory antibodies and stapled peptides that target the \textit{NOTCH1} transcriptional complex.\textsuperscript{59}

The \textit{NUP214-ABL1} fusion is mainly present in T lineage ALL expressing \textit{HOX11} or \textit{HOX11L2}. It recently appeared that imatinib mesylate could potentially be efficacious in these cases. Mammalian target of rapamycin (mTOR) acts as...
a nutrient sensor and regulator of translation in encoding proteins involved in regulating the G1 to S phase transition. Rapamycin and the second-generation mTOR inhibitors (temsirolimus, everolimus, deforolimus) form potentially synergistic combinations with doxorubicin and methotrexate and might modulate glucocorticoid resistance in T-ALL.60

The aberrant activation of JAK/STAT signalling in ETP ALL lymphoblasts suggests the JAK1/2 inhibitor ruxolitinib and the JAK3 inhibitor tofacitinib may be efficacious therapeutic agents in this setting.61 Bcl2 is another attractive target for therapy in immature subtypes of T cell lineage ALL.62

Philadelphia Chromosome Positive Acute Lymphoblastic Leukaemia

The Ph chromosome [t(9;22) (q34;q11)] is the most frequent cytogenetic abnormality in human leukaemia. It produces a fusion gene on chromosome 22, namely BCR-ABL. Patients with Ph-ALL represent approximately 25% of adult B lineage ALL patients. The management of adult Ph-positive ALL has been recently reviewed.63

Imatinib mesylate, a tyrosine kinase inhibitor (TKI) that targets BCR-ABL, is now an integral component of therapy for Ph-ALL. CR can be obtained in almost 95% of cases. The current consensus is that imatinib improves patient outcomes compared with historical control patients treated with chemotherapy alone. Efficacy analyses based on BCR-ABL transcript levels showed a clear advantage of the simultaneous over the alternating schedule.64 It also appeared important to maintain imatinib dose intensity during the initial phase of treatment.65 Furthermore, an induction regimen combining reduced-intensity chemotherapy and imatinib was recently validated in a randomised study in which it was compared with a standard imatinib/chemotherapy treatment.66 The rate of molecular remission increased from 5% to >50%, and the 5-year survival to ≥50%. The number of patients able to receive SCT, and the outcome of SCT, has improved.66 However, imatinib is ineffective at preventing or treating CNS involvement.67 Faster and deeper molecular responses can be achieved with second-generation TKIs (dasatinib and nilotinib), median MRD was lower and a better post-SCT outcome was observed.68 Dasatinib plus chemotherapy achieved CR in 96% of older patients with Ph-ALL.69 EFS was 41% at 3 years. The combination of nilotinib with high-dose cytotoxic drugs achieved high cumulative complete molecular remission and haematologic relapse-free survival rates.70 Ponatinib, a third-generation TKI targeting the T315I mutation which is resistant to imatinib and second-generation TKIs, is currently in development.71 The combination of chemotherapy (hyper-CVAD) with ponatinib is effective in achieving early sustained remissions with major molecular response in 95% of patients.72 The 2-year EFS rate was 81%. OS was similar with or without controlling for allogeneic SCT. Ponatinib was given at 45 mg daily for 14 days during induction and continuously at 30 mg thereafter until the achievement of complete molecular remission, and then at 15 mg daily indefinitely thereafter. New strategies, including dosing titration of ponatinib and optimised control of vascular risk factors, might further improve outcomes.

Allogeneic SCT in first CR remains the standard of care for adult Ph-ALL.73 Reducing BCR-ABL transcript levels has resulted in a lower pre-SCT leukaemia burden. Allogeneic SCT with myeloablative conditioning regimen overcomes MRD prior to SCT in some but not all studies. It is superior to allogeneic SCT after non-myeloablative conditioning regimen if MRD is not considered, but may be equivalent in patients with complete molecular response. Non-myeloablative allogeneic SCT approaches are therefore promising in patients with Ph-ALL.20 Treatment-related toxicity has been reported in 20–30% of cases with high rates of chronic GvHD.23,74 Prophylactic TKI given after engraftment may improve outcomes by preventing a resurgence of the leukaemic clone.75 However, the optimal duration of this treatment has not yet been established. In MRD-positive patients, imatinib at 400 mg/day has been shown to prevent relapse and to achieve molecular remission in 52% of cases after 1.5 months of treatment.76 However, imatinib is sometimes poorly tolerated after allogeneic SCT and should either be discontinued or the dose reduced.77 The median duration of negative MRD in patients with post-transplant imatinib administration has been reported as 6 months when imatinib was administered upon detecting MRD after allogeneic SCT compared with 12 months when imatinib was given as soon as possible after allogeneic SCT.78 Reappearance of BCR-ABL1 transcripts early after SCT identifies a small subset of patients who do
not benefit sufficiently from imatinib, and in whom alternative approaches should be explored.\textsuperscript{79} Alternative therapies could be considered in patients who remain positive for BCR-ABL transcripts more than 2 months after starting imatinib therapy following transplant. Blinatumomab has shown promising results in patients with high-risk ALL.\textsuperscript{38} Activity has been demonstrated in Ph-ALL with T315I mutation.\textsuperscript{80} CR was achieved in 36% of all cases and in 40% of patients with mutation T315I. Preliminary results indicate that treatment with blinatumomab is able to convert MRD-positive ALL into a MRD-negative status. Eighty-eight percent of patients achieved a complete MRD response.\textsuperscript{80}

Alternative donors may be considered for patients lacking a matched related or matched unrelated donor. Haploidentical SCT represents an encouraging treatment option.\textsuperscript{81} The incidence of non-relapse mortality was similar between the patients who received HLA-matched donor cells and those who received haploidentical donor cells. The incidence of cytomegalovirus infection was, however, significantly higher in the latter group. Haploidentical SCT reduced the relapse rate. The status of umbilical cord blood transplantation in adults with Ph-ALL is not well established. Recent analyses showed that MRD-positivity before umbilical cord blood transplantation was associated with increased relapses.\textsuperscript{82} Autologous SCT remains a possible therapeutic option when MRD is not present before the procedure.\textsuperscript{66} Results of autologous SCT have significantly improved in the era of TKIs.\textsuperscript{83,84} however there is no consensus on how best to use TKIs after autologous SCT.

**BCR-ABL-LIKE Acute Lymphoblastic Leukaemia**

Leukaemic cells from many patients with B cell lineage ALL lack known chromosomal alterations. A new entity of high-risk B cell precursor ALL has been recently described, namely ‘Ph-like’ ALL or ‘BCR-ABL1-like’ ALL which is defined by a more similar gene signature than Ph-ALL without BCR-ABL translocation. This subtype represents up to 25% of adolescent and young adult ALL and is associated with a poor outcome, but incidence does not increase with age.\textsuperscript{85} Comparative genomic hybridisation arrays and molecular cytogenetics are necessary for the diagnosis. However, validation of a robust gene expression classifier is still warranted for a routine clinical use.\textsuperscript{86} More than 80% of Ph-like ALL cases have abnormalities in genes involved in B cell development, such as IKZF1 deletions which facilitate leukaemia transformation by inducing constitutive kinase activation and signalling through the activation of ABL1 and/or JAK/STAT pathways,\textsuperscript{87} and CLRF2 overexpression and tyrosine kinase activating rearrangements involving ABL1, JAK2, PDGFRB, and several other genes.\textsuperscript{88} The gene expression profile of IKZF1-mutated, BCR-ABL1-negative ALL is enriched for haematopoietic stem cell genes and exhibits decreased expression of B cell receptor signalling and differentiation genes.\textsuperscript{88}

Preclinical results in Ph-like ALL have suggested a potential role of a targeted therapeutic strategy according to the molecular profile of leukaemia cells.\textsuperscript{89,90} Recently, several cases have been reported with responses to TKIs (imatinib or dasatinib).\textsuperscript{91,92} Fifty percent of Ph-like ALL shows activation of JAK-STAT and PI3K/mTOR pathways and should also be sensitive to JAK2 (ruxolitinib) and mTOR inhibitors.\textsuperscript{89,90,93}

**Mixed-Lineage Leukaemia-Rearranged Acute Lymphoblastic Leukaemia**

ALL carrying a chromosomal translocation involving the mixed-lineage leukaemia (MLL) gene on chromosome segment 11q23 or displaying a MLL-rearranged ALL in their molecular biology have a particularly poor prognosis. ALL with MLL translocations can be separated from conventional ALL. Immunophenotypic differences include a lack of the early lymphocyte antigen CD10, expression of proteoglycan NG2, and the propensity to co-express myeloid antigens. MLL shows a gene expression profile markedly different from that of conventional ALL.\textsuperscript{94} These include genes expressed in early B cells (MME, CD24, CD22, DNTT), genes required for appropriate B cell development (TCF3, TCF4, POU2AF1, LIG4), and genes correlated with B precursor ALL (SMARCA4). Genes encoding for adhesion molecules are relatively over-expressed in MLL-rearranged ALL (LGALS1, ANXAI, ANXA2, CD44, SPN). Genes that are expressed in progenitors (PROML1, FLT3, LMO2), myeloid-specific genes (CCNA1, SER-PINB1, CAPG, RNASE3), and natural killer cell-associated gene (NKG2D) are also highly expressed in MLL-rearranged ALL.

As MLL normally regulates the expression of HOX genes, its role in leukaemogenesis may include altered patterns of HOX gene expression.

Patients with MLL-rearranged ALL are highly resistant to steroids and L-asparaginase, but sensitive to nucleoside analogue drugs such as cytarabine, cladribine, and clofarabine,\textsuperscript{95} suggesting...
‘acute myeloid leukaemia-like’ chemotherapy courses may be efficacious in this type of leukaemia. Allogeneic SCT is still considered to play an important role as a consolidation therapy. However, patients achieving MRD negativity pre-SCT had better outcomes than those with persistent MRD pre or post-SCT.96 MLL fusion proteins aberrantly recruit epigenetic regulatory proteins, including histone deacetylases, histone methyltransferases, bromodomain-containing proteins, and transcription elongation factors to mediate chromatin remodelling and regulate tumourigenic gene expression programmes. Histone deacetylases inhibitors, such as panobinostat, and cyclin-dependent kinase inhibitors were potent inducers of apoptosis in MLL-rearranged cells.97 Combined MEK and VEGFR-2 inhibition strengthened the reduction in MLL-rearranged leukaemia cell survival by blocking the Akt/mTOR and MAPK pathways simultaneously.98 Inhibitors of the protein methyltransferase DOT1L have also shown efficacy as single-agents and synergistically with other chemotherapeutics and hypomethylating agents.99 AMPK inhibition, including endothelial nitric oxide synthetase and BCL-2 inhibition, was shown to synergistically enhance the antiproliferative effects of chemotherapy in MLL-rearranged cell lines.100 Combining all-trans retinoic acid with cytarabine has also shown a synergistic anti-leukaemic effect in MLL-rearranged-positive cells.101 FLT3 expression identifies MLL-AF4+ ALL patients at very high-risk of treatment failure, emphasising the potential value for FLT3 inhibitors.102 These findings highlight a new therapeutic approach to potentially overcome the resistance of MLL-rearranged ALL to conventional chemotherapies.

CONCLUSIONS AND PERSPECTIVES

Due to risk-stratified treatment, more optimised treatment protocols, and improved supportive care, the 5-year EFS on contemporary treatment protocols in adult ALL is approaching 50%. Treatment is relatively well structured with the development of risk-adapted therapies and paediatric-like protocols and by standardisation and monitoring of MRD. Advances in the management of adult ALL including the identification of novel sub-entities, the evaluation of MRD, and the use of new targeted therapies has progressively led to a more personalised treatment approach in adult ALL.

Genomic analysis represents a major advance for identifying the genetic basis of leukaemogenesis and disease relapse in ALL. Sensitive detection of mutations during therapy is important to track progression and adjust therapy. Relapse usually arises from a minor clone unless relapse-enriched mutations are already present. Early detection of minor clones may guide prediction of relapse. Genomic analysis has been especially important for T cell ALL and raised new challenges, such as to better understand how T cell oncogenes and tumour suppressors co-operate to drive overt disease; to determine the exact order in which genetic lesions are acquired during initiation, progression, and maintenance of the disease; to determine the exact cell of origin for T cell transformation, and the molecular mechanism that regulates pre-leukaemic stem cell activity of thymic precursors; and to determine the oncogenic contributions of deregulated microRNAs, long non-coding RNAs, enhancer activities, chromatin remodelling, and epigenetic changes in the setting of malignant T cell transformation.

Molecular targets can be identified in the vast majority of patients with adult ALL. MRD is currently the main prognostic factor. MRD methodology and terminology need standardisation. MRD can be identified at different times in the disease and potentially allow risk stratification. However, MRD relevance at any time-point is dependent on specific prior therapy and possibly cannot be extrapolated from one protocol to another.

Further studies need to address how new drugs should be combined with up-front chemotherapy and how this can be reduced to minimise side effects without jeopardising clinical outcome. Harmonising the backbone of chemotherapeutic protocols of different study groups should also be beneficial for performing clinical trials with new drugs in rare subsets of patients and accelerate the development of those drugs in co-operation with pharmaceutical companies.

Advances have been particularly prevalent over the last few years in Ph-ALL. Less chemotherapy intensity in induction prior to SCT was shown not to be inferior, while initial dose intensity of TKI was demonstrated as important. Second and third-generation TKIs improved results in terms of MRD, but there are no prospective randomised trials on outcome. Overall, SCT is still superior to no SCT, but subsets of patients (perhaps likely defined by MRD) may do well long-term
without allogeneic SCT. Furthermore, it has been suggested that a lower number of patients with Ph-ALL need allogeneic SCT when treated with second-generation TKIs. After molecular response achievement, autologous SCT or chemotherapy plus TKI yielded similar results to those seen following allogeneic SCT. Further questions in Ph-ALL should focus on the reduction of allogeneic SCT indications and whether a chemo-free strategy could become a reality with the incorporation of other targeted therapies, such as monoclonal antibodies and immunotherapy.

Allogeneic SCT still remains a major issue in the treatment of adult ALL. There are recent trends showing an increased use of reduced-intensity conditioning and alternative donors. Issues to be investigated with reduced-intensity conditioning include the optimal chemotherapy to be applied prior to reduced-intensity conditioning, the optimal type of conditioning regimen to be used, and how to improve quality of life. Designing maintenance strategies after reduced-intensity conditioning allogeneic SCT may further improve the outcome. The role of alternative donors is yet to be established. MRD and molecular marker analyses should in time modify therapeutic strategies.

New monoclonal antibodies and immunotherapy tools are currently changing the landscape of ALL therapy. However, many questions remain: challenges with CAR T cells including definition of the optimal CAR design and effector cell population; how to modulate immunotoxicity without losing efficacy; defining the optimal placement of CAR therapy either as bridge to SCT or alternative to SCT; defining the optimal therapeutic strategy with administration in relapse or after remission achievement; and defining when it should be given in relation to chemotherapy. Another major issue with such treatments is the cost and the complexity of manufacture.

Over the coming years, the treatment of adult ALL will certainly change from disease-type to molecular-target type and from risk-stratified treatment schedules to more personalised therapies. More specific therapies and new immunotherapy-based approaches are the most promising advances for improving prognosis and reducing treatment-related morbidity.

REFERENCES


33. Sasaki K et al. Phase II study of the frontline Hyper-CVAD in combination with ofatumumab for adult patients (pts) with CD20 positive acute lymphoblastic leukemia (ALL). Blood. 2015;126(23):1295.


54. Kako S et al. Meta-analysis and meta-regression analysis to compare the outcomes of chemotherapy for T- and B-lineage acute lymphoblastic leukemia (ALL); the use of dexamethasone, L-asparaginase, and/or methotrexate may improve the outcome of T-lineage ALL. Ann Hematol. 2016;95(1):87-92.

55. DeAngelo DJ et al. Nelarabine induces


60. Techeey DT et al. mTOR inhibitors are synergistic with methotrexate: an effective combination to treat acute lymphoblastic leukemia. Blood. 2008;112(5):2020-3.


64. Rousselot P et al. Dasatinib (Sprycel®) and low intensity chemotherapy for first-line treatment in patients with de novo Philadelphia positive ALL aged 55 and over: final results of the EWAL-Ph-01 study. 666. 54th ASH Annual Meeting and Exposition, 8th-12th December, 2012.


101. Sakamoto K et al. Sensitivity of MLL-rearranged AML cells to all-trans retinoic acid is associated with the level of H3K4me2 in the RARα promoter region. Blood Cancer J. 2014;4:e205.


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