MADRID
22ND CONGRESS
JUNE 22 - 25 | 2017
European Hematology Association

Acute lymphoblastic leukemia - The worst and the best - Section 3

Novel approaches with recently licensed drugs or recently studied in relapsed acute lymphoblastic leukemia

Josep-Maria Ribera

Clinical Hematology Department, ICO-Hospital Germans Trias i Pujol, Josep Carreras Research Institute, Universitat Autònoma de Barcelona, Spain

Take-home messages

- Although acute lymphoblastic leukemia is highly curable with conventional chemotherapy (ALL), novel therapeutic approaches are still needed to improve outcomes for high-risk or relapsed ALL, especially in adults.
- Immunotherapeutic approaches have significantly improved the outcome of R/R ALL patients and are currently tested in early phases of the disease.
- Targeted therapy combined with conventional chemotherapy and/or immunotherapy can provide promising results in some specific subtypes of ALL.

Most drugs used in standard regimens for acute lymphoblastic leukemia (ALL) were developed more than 30 years ago and have contributed to the success of treatment, especially in children. Since that time, several new drugs have been developed and incorporated into ALL treatment. However, a small number of drugs have been approved by the regulatory agencies since the year 2000, including imatinib (2001), clofarabine (2004), nelarabine (2005), dasatinib (2006), liposomal vincristine sulfate (2012), ponatinib (2012) and blinatumomab (2014). In spite of this, novel therapeutic approaches are still needed to improve outcomes for high-risk or relapsed ALL, especially in adults. These include purine nucleoside analogs, mammalian target of rapamycin (mTOR) inhibitors, proteasome inhibitors, histone deacetylase (HDAC) inhibitors, hypomethylating agents, Bruton's tyrosine kinase (BTK) inhibitors, Janus kinase-signal transducer and activator of transcription (JAK-STAT) inhibitors, anti-programmed cell death protein (anti-PD-1) antibodies, mitogen-activated protein kinase (MEK) inhibitors, CXCR4 antagonists, poly (ADP-ribose) polymerase (PARP) inhibitors, and FMS-like tyrosine kinase 3 (FLT3) inhibitors, among others.[1] The immunotherapeutic approaches with monoclonal antibodies, antibody drug conjugates and bispecific antibodies have shown very promising results in relapsed or refractory ALL patients.[2] Apart of these drugs, therapeutic strategies harnessing T lymphocytes or NK cells have been developed, being the CAR T cells associated to an impressive short-term efficacy.[3] On the other hand, progress in the genetic characterization of ALL in both children and adults has allowed the recognition of specific subtypes with specific altered pathways targetable with specific drugs. Philadelphia chromosome-positive ALL was the first example of an ALL subtype in which the combination of tyrosine kinase (TKI) inhibitors with standard chemotherapy resulted in a significant improvement in the patients' survival. Similarly, the patients with the BCR-ABL like ALL subtype are currently enrolled in clinical trials with TKI inhibitors (e.g., dasatinib) or JAK inhibitors (e.g., ruxolitinib) combined with chemotherapy, depending on their mutational profile.[4] Progresses in the knowledge of the biology of MLL-rearranged ALL have led to evaluate the activity of hypomethylating drugs (eg, azacitidine), DOT1L inhibitors (e.g., EPZ5676), FLT3 inhibitors, MEK inhibitors or BCL-2 inhibitors, in combination with chemotherapy.[5]

Some of the novel approaches with recently licensed or recently studied drugs in relapsed or in newly diagnosed ALL have been associated with significant improvement in survival in phase 2 or phase 3 clinical trials. For mature B ALL, there is no doubt that the combination of rituximab with specific chemotherapy constitutes the treatment of choice.[6] Similarly, significant improvements in event-free survival have been observed with the incorporation of rituximab to the standard chemotherapy schedule in B-cell precursor (BCP) ALL with CD20 expression.[7] In patients with relapsed or refractory (R/R) BCP ALL two phase 3 studies with inotuzumab[8] ozogamycin and blinatumomab[9], respectively, have demonstrated significant improvement in the complete remission (CR) rate and the overall survival (OS) compared with standard of care (SOC) chemotherapy and these therapies should be currently considered as a bridge to hematopoietic stem transplantation (HSCT) in these patients. A global phase 2 study with blinatumomab in patients with minimal residual disease (MRD) positive ALL has shown 80% rate of molecu-

Acute lymphoblastic leukemia - The worst and the best - Section 3

Table 1. Antileukemic drugs in current clinical trials in acute lymphoblastic leukemia.

Class agent	Target	Indication
Purine nucleoside analogue		
Clofarabine	Ribonucleotide reductase; DNA Polymerase; mitochondria	All ALL
Nelarabine	Ribonucleotide reductase; DNA synthesis	T-ALL
Vinca alkaloid		
Vincristine sulfate liposome	Tubulin	All ALL
Kinase inhibitors		
ABL1 kinase inhibitors (dasatinib, ponatinib)	ABL1 kinase; PDGFR-B	BCR-ABL+ ALL
Aurora kinase inhibitors (alisertib)	Aurora A kinase	BCR-ABL-like ALL
Janus kinase inhibitors (JAK)	JAK	BCR-ABL+ ALL
Ruxolitinib, tofacitinib, other		JAK-mutated ALL
BCR-ABL-like ALL		
T-ALL		
Tyrosine kinase inhibitors	FMS-like tyrosine kinase 3 (FLT3)	MLL-ALL
Lestaurtinib, midostaurin, sorafenib, quizartinib, tandutinib, sunitinib		Hyperdiploid ALL
Other molecular or signaling inhibitors		
Proteasome inhibitors (bortezomib)	Ubiquitin pathway	All ALL
mTOR inhibitors (sirolimus, everolimus)	mTOR	All ALL
FT inhibitors (tipifarnib, lonafarnib)	Ras, lamin A	All ALL
γ secretase inhibitors	γ Secretase	T-ALL
Angiogenesis inhibitors (bevacizumab)	VEGF	All ALL
Apoptosis inducers (obatoclax, oblimersen)	Bcl-2	All ALL
CXCR4 antagonists	CXCL12(SDF1)/CXCR4 axis	All ALL
B-cell receptor inhibitors	Ibrutinib, idelalisib, other BTK inhibitors	B-precursor ALL
Epigenetic therapy		
DNA methyltransferase inhibitor (Azacitidine, decitabine)	DNA methyltransferase	All ALL
Histone methyltransferase inhibitor (EPZ-5676)	DOT1L	*MLL*-ALL
HDAC inhibitor (Vorinostat, panobinostat)	Histone deacethylase	All ALL
Immune therapy		
Monoclonal antibody		
Blinatumomab	*CD19 (engages CD3)*	CD19+ ALL
Coltuximab ravtansine	*CD19*	CD19+ ALL
Denintuzumab mafodotin	*CD19*	CD19+ ALL
DT2219ARL	*CD19 and CD22*	CD19/CD22+ ALL
Rituximab	*CD20*	CD20+ ALL
Epratuzumab,	*CD22*	CD22+ ALL
Moxetumomab pasudotox	*CD22*	CD22+ ALL
Inotuzumab ozogamycin	*CD22*	CD22+ ALL
Alemtuzumab	*CD52*	CD52+ ALL
Brentuximab vedotin	*CD30*	T-ALL
Cellular therapy		
NK cells	KIR ligand	
T cells with CD19 chimeric Ag receptor	*CD19*	CD19+ ALL
T cells with CD22 chimeric Ag receptor	*CD22*	CD22+ ALL
T cells with CD123 chimeric Ag receptor	*CD123*	CD19 negative relapses

lar response, being translated into improved OS, independent of the subsequent HSCT realization.[10] Another phase 2 study with blinatumomab in R/R Ph+ ALL has shown a CR rate of 36%, independent of the ABL mutation status.[11] Blinatumomab and inotuzumab are currently being investigated in newly diagnosed patients with BCP ALL, integrated with the chemotherapy schedule, especially during consolidation. In this sense, two ongoing phase 2 studies with inotuzumab combined with attenuated chemotherapy have shown promising results in adults and elderly patients with R/R or with newly diagnosed BCP ALL, respectively.[12,13]

Among the non-immunochemotherapeutic drugs, the combination of ponatinib with chemotherapy has shown very promising short-term results in patients with newly diagnosed Ph+ ALL,[14] being superior to those obtained with imatinib in historical comparisons.[15] If these results are confirmed in other ongoing trials this combination could be the treatment of choice for these patients. Other non-TKI approaches (e.g., allosteric inhibitors) are actively investigated. Current trials are evaluating the combination of immunotherapeutic drugs (e.g., blinatumomab) with TKI inhibitors in an attempt to treat Philadelphia chromosome-positive ALL with a non-chemotherapeutic approach.

Some approved drugs and drugs under development are actively investigated in phase 2 and phase 3 clinical trials. In this sense, randomized studies compare first-line chemotherapy with standard vincristine versus vincristine sulfate liposome in newly diagnosed Ph-negative ALL patients.[16] Clofarabine is currently being tested as part of the conditioning regimens for allogeneic HSCT in ALL patients.[17] Proteasome inhibitors are actively investigated in patients with R/R ALL (Table 1).

The therapeutic armamentarium with new drugs for T-ALL is limited. Nelarabine has been safely integrated into intensive chemotherapy regimens in newly diagnosed T-cell ALL in children and in adults, although more information is needed to know whether the addition of nelarabine improves their outcome.[18] Targeting NOTCH (gamma-secretase inhibitors), the IL7R-JAK1/3-STAT5 axis (ruxolitinib, tofacitinib), the PI3K/Akt/mTOR axis (PI3K or mTOR inhibitors), the NUP214-ABL1 rearrangement (dasatinib) or BCL2 (BCL2 inhibitors, ETP ALL) are promising areas of research.[19,20]

References

1. Man LM, Morris AL, Keng M. New Therapeutic strategies in acute lymphocytic leukemia. Curr Hematol Malig Rep 2017 doi: 10.1007/s11899-017-0380-3.
2. Maino E, Bonifacio M, Scattolin AM, Bassan R. Immunotherapy approaches to treat adult acute lymphoblastic leukemia. Expert Rev Hematol 2016;9:563-77.
*3. Aldoss I, Bargou RC, Nagorsen D, et al. Redirecting T cells to eradicate B-cell acute lymphoblastic leukemia: bispecific T-cell engagers and chimeric antigen receptors. Leukemia 2017;31:777-87.

Excellent review of the antileukemic use of redirected T cells.

*4. Roberts KG, Gu Z, Payne-Turner D, et al. High Frequency and Poor Outcome of Philadelphia Chromosome-Like Acute Lymphoblastic Leukemia in Adults. J Clin Oncol. 2017;35:394-401.

Excellent paper on the biology ad possible therapies for BCR-ABL like ALL.

5. Guest EM, Stam RW. Updates in the biology and therapy for infant acute lymphoblastic leukemia. Curr Opin Pediatr 2017;29:20-6.
6. Ribrag V, Koscielny S, Bosq J, et al. Rituximab and dose-dense chemotherapy for adults with Burkitt's lymphoma: a randomised, controlled, open-label, phase 3 trial. Lancet 2016;387:2402-11.
7. Maury S, Chevret S, Thomas X, et al. Rituximab in B-lineage adult acute lymphoblastic leukemia. N Engl J Med. 2016;375:1044-53.
*8. Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med. 2016;375:740-53.

Phase 3 study showing superiority of inotuzumab over standard of care therapy in relapsed/refractory CD22 positive ALL.

*9. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376:836-47.

Phase 3 study showing superiority of blinatumomab over standard of care therapy in relapsed/refractory CD19 positive ALL without the Philadelphia chromosome.

10. Gökbuget N, Dombret H, Bonifacio M, et al. Long-term outcomes after blinatumomab treatment: Follow-up of a phase 2 study in patients (Pts) with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukemia (ALL). Blood 2015;126:680(abstract).
11. Martinelli G, Boissel N, Chevallier P, et al. Complete hematologic and molecular response in adult patients with relapsed/refractory philadelphia chromosome-positive b-precursor acute lymphoblastic leukemia following treatment with blinatumomab: Results from a phase II, single-arm, multicenter study. J Clin Oncol 2017. doi: 10.1200/JCO.2016.69.3531.
12. Sasaki K, Jabbour EJ, O'Brien SM, et al. Phase II study of the salvage Mini-Hyper-CVD in combination with inotuzumab ozogamicin (INO) for adult patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL). Blood 2013;127:1606 (abstract).
13. Sasaki K, Jabbour EJ, O'Brien SM, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy (mini-hyper-CVD) As frontline therapy for older patients with acute lymphoblastic leukemia (ALL): Interim result of a phase II clinical trial. Blood 2016;127:588 (abstract).
14. Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. Lancet Oncol 2015;16:1547-55.
15. Sasaki K, Jabbour EJ, Ravandi F, et al. Hyper-CVAD plus ponatinib versus hyper-CVAD plus dasatinib as frontline therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: A propensity score analysis. Cancer 2016;122:3650-6.
16. Douer D. Efficacy and safety of vincristine sulfate liposome injection in the treatment of adult acute lymphocytic Leukemia. Oncologist 2016;21:840-7.
17. Kebriaei P, Bassett R, Lyons G, et al. Clofarabine plus busulfan is an

Acute lymphoblastic leukemia - The worst and the best - Section 3

effective conditioning regimen for allogeneic hematopoietic stem cell transplantation in patients with acute lymphoblastic leukemia: Long-term study results. Biol Blood Marrow Transpl 2017;23:285-92.

18. Winter SS, Dunsmore KP, Devidas M, et al. Safe integration of nelarabine into intensive chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group Study AALL0434. Pediatr Blood Cancer 2015;62:1176-83.
19. Litzow MR, Ferrando AA. How I treat T-cell acute lymphoblastic leukemia in adults. Blood 2015;126:833-41.
*20. Marks DI, Rowntree C. Management of adults with T-cell lymphoblastic leukemia. Blood 2017; 129: 1134-42.

Excellent review of the therapy of T-cell ALL in adults.