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REVIEW

Drugs under preclinical and clinical study for treatment of acute and chronic lymphoblastic leukemia

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Abstract: Targeted therapy has modernized the treatment of both chronic and acute lymphoblastic leukemia. The introduction of monoclonal antibodies and combinational drugs has increased the survival rate of patients. Preclinical studies with various agents have resulted in positive outputs with Phase III trial drugs and monoclonal antibodies entering clinical trials. Most of the monoclonal antibodies target the CD20 and CD22 receptors. This has led to the approval of a few of these drugs by the US Food and Drug Administration. This review focuses on the drugs under preclinical and clinical study in the ongoing efforts for treatment of acute and chronic lymphoblastic leukemia.

Keywords: targeted therapy, monoclonal antibodies, preclinical studies, receptors, lymphoblastic leukemia

Background

Acute lymphoblastic leukemia (ALL) is a very common malignancy of childhood and adolescence.[1] Two-thirds of patients with ALL are children or adolescents.[2] ALL is the major cause of death related to hematological malignancies.[3] Chronic lymphoblastic leukemia (CLL) is a disease of B-cell accumulation, which is common in adults.[4] The response and survival rate of treatment with drugs currently in practice is limited and hence there is a need for modernized drugs.[5] Such drugs should be target-specific for effective treatment. Numerous target-specific drugs are being screened and some of them are in preclinical and clinical phases. This review intends to summarize the recent advances in such studies.

Preclinical trials related to lymphoblastic leukemia

Various preclinical agents applied in the treatment of leukemia are summarized in this section. Several novel chemotherapeutic agents have been tested for their preclinical efficacy in leukemia cell lines. Z36, an inhibitor of Bcl-xL, was effective against ALL Jurkat cells. The authors suggest the role of autophagy resistance to be a major criterion for further anticancer studies with the inhibitor.[6]

Chemotherapeutic drugs that are considered clinical are being used in combination as preclinical agents for treating leukemia cell lines. Rapamycin, a macrolide of bacterial origin, was shown to inhibit the growth of cancerous cells by impeding the transcription of the polymerases and resulting in its autophagy in pre-B ALL cells.[7] The combination of dexamethasone and rapamycin effect was more sound compared to individual effect. In vitro analysis in T-lineage cell lines with PTEN mutation and in

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vivo analysis with mice carrying PTEN-mutated xenografts elucidated the efficacy.[8]

Natural compounds of plant origin were also included in the investigations performed for the treatment of ALL. 1-Methoxybrassinin, a phytoalexin, induced apoptosis and caused an arrest in cell cycle in Jurkat cells.[9] In CLL cells, silverstrol induced cell death by translational inhibition of Mcl-1 with consequent mitochondrial damage, as illustrated by generation of reactive oxygen species (ROS) and membrane depolarization.[10] Zerumbone, a natural compound from *Zingiber zerumbet* Smith, was used against ALL and proved that it was able to induce apoptosis in the cancer cells.[11] *Dunaliella salina*, belonging to green algae, showed antileukemic effects in syngeneic leukemia-implanted mice (BALB/c and WEHI-3). It increased the T-(CD3) and B-cell (CD19) population, increased phagocytosis mediated by macrophages, and enhanced cytotoxicity.[12] Leaf and stem callus cultures of *Salvia miltiorrhiza* Bunge, one of the widely used Chinese medicinal herbs, were cytotoxic to CCRF-CEM ALL cells.[13] Fermented brown rice extract has been shown to possess anticancer effects in vitro against human ALL cells (Jurkat cells, RCB3052) by induction of apoptosis.[14] A lead compound of monoterpene origin induced caspase-dependent apoptosis in B-cell ALL models such as Nalm06 and SEM cells.[15] A diterpene, casearin J, due to sarcoendoplasmatic reticulum calcium ATPase pump inhibition, was able to induce depletion of the calcium pools of endoplasmic reticulum, oxidative stress, and apoptosis through the intrinsic signaling pathway in CCRF-CEM, CEM-ADR5000, and Jurkat cells.[16] These studies suggest that phytochemicals could be effective preclinical agents to treat ALL and CLL.

Microbial proteins are also under investigation for their potential efficacy in treating ALL and CLL. A leukotoxin (LtxA) from the oral bacterium *Aggregatibacter actinomycetemcomitans* preferentially killed the malignant white blood cells (WBCs), whereas the normal WBCs were considerably resistant. In severe combined immunodeficiency (SCID) mouse model, LtxA was efficient in increasing the mean survival time of the mice.[17] Smac mimetic LCL161, a small molecular antagonist of the inhibitor of apoptosis, is a protein of viral origin. It has been used in combination with Erastin, buthionine sulfoximine, or Auranofin and caused cell death in human T-ALL (Jurkat, Molt-4) and precursor (pre)-B-ALL (Reh, Tanoue) cell lines by inhibition of antioxidant defense mechanisms. This happened through induction of ROS production and lipid peroxidation since ROS scavengers or inhibitors of lipid peroxidation can prevent cell death.[18] In yet another in vitro study with a different set of Smac mimetics, cell death was induced in ALL cells by apoptotic and necroptotic pathways.[19]

With regard to nanotherapy, ZnPc-loaded poly (methyl methacrylate) nanoparticles were found to exert antiapoptotic effects in Jurkat cells.[20] Polyvalent aptamers-modified gold nanoparticles were cytotoxic to Molt-4 (C149, T-cell line, human ALL) cells in vitro.[21] In RNAi-based studies, a gene named NANOG was found promoting apoptosis and arresting cell cycle though p53-dependent pathway, resulting in controlled cell proliferation and decreased self-renewal.[22]

Monoclonal antibodies are synthesized by immune cells, and can bind to specific epitopes on cancer cells. This will induce immunological response against the specific type of cancer. The use of monoclonal antibodies alone or in combination with other chemotherapeutic agents increase target-specificity and efficacy. The conjugate of HD37 with daunorubicin and vincristine was effective as it induced apoptosis in 30% of the three Pre-B ALL cell lines used for the study and increased the mean survival time in SCID/ALL mice.[23] The antibody drug conjugate of HB22.7 (anti-CD22 antibody) and saporin (ribosome-inhibiting protein) were found to be cytotoxic in vitro and increased the mean survival time in vivo from 20 to more than 50 days in nonobese diabetic/severe combined immunodeficiency (NOD/SCID) xenograft mouse model when compared to control.[24] Adoptive immunotherapy with a panel of humanized scFvs (single-chain variable fragment), a particular group of chimeric antigen receptors targeting CD19, resulted in antileukemic effect in vivo in NOD/SCID mouse xenotransplant model.[25]

Testin is a protein product of *TES* gene located on chromosome 7. In a most recent report, the re-expression of Testin through plasmid transfection resulted in rapid cell death or cell-cycle arrest.[26]

Human trials those sound effective ALL

Imatinib, a chemotherapeutic drug designed to selectively inhibit the tyrosine kinases, was used to treat 69 patients having Ph+ ALL. Twenty-four of them were pretransplant, nine were posttransplant, and eleven were both pre- and posttransplant. The 3-year estimated overall survival (OS) was 62.3%.[27] Seventy-two patients with a median age of 55 years received dasatinib with eight cycles of alternating hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, and high-dose cytarabine and methotrexate. The median disease-free survival and OS were 31 and 47 months, respectively.[28] Thirty-seven patients with

a median age of 51 years received ponatinib. The median follow-up was 26 months with 2-year event-free and OS rates of 81% and 80%, respectively.[29]

Blinatumomab, a monoclonal antibody specific to CD19 and CD3, was given to 38 patients, who were divided into six cohorts for three cycles of 4 weeks, with 2 weeks interim. The overall response rate (ORR) observed was 28.9%.[30] Another study with the same agent showed complete response rate (CRR) of 95% for primary relapse and 40% for subsequent relapses. The median survival was 9.8 months.[31] Inotuzumab ozogamicin is another monoclonal antibody that targets CD22 antigen. Forty-nine patients, aged 6–80 years, with refractory or relapsed ALL, intravenously received inotuzumab ozogamicin alone at a dose of ~1.8 mg/m^2 an hour, every 3 weeks. Response was observed in 57% of the total patients studied, with a median OS of 5.1 months and the responder survival of 7.9 months. Abnormalities in liver function were observed in 25% of the cases but were harsh only in half of the patients with abnormality. The results were supportive of inotuzumab ozogamicin when compared to chemotherapy with higher OS. In elderly patients, aged 60 and above, inotuzumab ozogamicin with chemotherapy resulted in 90% OS.[32] In a Phase II study with coltuximab ravtansine, a CD19-targeting antibody–drug conjugate, 36 patients were chosen, of whom 17 were evaluable. Of the 17 patients, four had an ORR of 25.5% over a duration of response of 1.9 months.[33]

CLL

Conventional chemotherapy

When treated with bendamustine alone, the ORR varied within the range of 56%–93%, with a CRR of 7%–30%. The unfavorable effects of treatment with bendamustine were nausea, allergic reactions, infection, and diarrhea.[34] In Phase III trials, bendamustine at the dose of 100 mg/m^2 to 319 patients for six cycles of 28 days showed higher ORR (68%), CR (31%), and median progression-free survival (PFS) of 21.6 months. Hence, the US Food and Drug Administration approved it as a drug for CLL in 2008.[35] Ibrutinib put 2.7% CLL cells to death in the lymph node by possibly interfering in migration, adhesion, and egression. In the 31 patients tested, the ORR was 33% in patients with M-CLL and 77% in patients with U-CLL.[36] Taken as a whole, there was no positive response related to survival at the end of Phase II trials with oblimersen sodium. Yet, there were optimistic outcomes with patients who responded to the oblimersen, a Bcl-2 inhibitor. Patients of older age or with relapsed disease can be treated with oblimersen in combination with other potential agents such as antibodies or kinase inhibitors for the reason that it is less toxic.[4]

Targeted chemotherapy

When rituximab, a monoclonal antibody specific to CD20 antigen, was given intravenously at 375 mg/m^2 each week consecutively for 4 weeks, a 9% CR, 58% ORR, and 18.6 months PFS was observed.[37] Obinutuzumab, another monoclonal antibody that targets CD20 antigen, given in a Phase III trial to 671 patients in combination with chlorambucil resulted in median PFS of 26.7 months. OS also improved with treatment. Infusion-related reactions occurred among 66% of the patients.[38] Ofatumumab is also a monoclonal antibody specific to CD20 antigen. In a study involving 103 patients treated with Ofatumumab, the grade 3–4 toxicities noted were neutropenia, thrombocytopenia, anemia, pneumonia, and fever. The ORR was 22%. The OS was 11 months with low CRR.[39]

Combinatorial therapy

Idelalisib, an inhibitor of phosphatidylinositol-3-kinase δ, is used in combination with rituximab. The median PFS was not reached for idelalisib in combination with rituximab, given to 220 patients. The ORR was 81%. The OS was 92% at 12 months. The associated adverse effects were observed in 40% of the patients.[40] Currently, CLL is treated with fludarabine, cyclophosphamide, and rituximab-based chemoimmunotherapy.[4]

The combination of chlorambucil and rituximab given to 321 patients showed a median PFS of 15.2 months. The ORR was 65% and the CR rate was 7%. The treatment of 336 patients with chlorambucil and obinutuzumab resulted in median PFS of 26.7 months. The ORR was 78% and the CR rate was 21%.[41] In combination with bendamustine, obinutuzumab resulted in 90% ORR and 20% CR rate in 20 patients; in combination with fludarabine cyclophosphamide, obinutuzumab resulted in 62% ORR and 10% CR rate in 21 patients.[42]

Lumiliximab, the anti-CD23 antibody, in combination with fludarabine, cyclophosphamide, and rituximab resulted in median PFS of 28.7 months for 31 patients. The ORR and CR were 65% and 52%, respectively.[43] Rituximab in combination with navitoclax for 12 weeks resulted in 55% ORR and prolonged PFS. The same combination given as treatment until disease progression or unacceptable toxicity resulted in 70% ORR.[44] The 13 patients enrolled for treatment with obatoclax, fludarabine, and rituximab showed an ORR of 85% with 15% CR and 20 months of median time to progression.[45]

Conclusion

ALL and CLL comprise an assemblage of patients with exclusive characteristics. Novel treatment modes include monoclonal antibodies alone and in combination with certain agents that can act on blasts. The survival rate of patients treated with these novel therapeutic agents has increased recently. In the near future, it is expected that monoclonal antibodies will play a major role in the treatment of ALL and CLL by targeting characteristic receptors to the specific type of disease.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Jiménez-Hernández E, Jaimes-Reyes EZ, Arellano-Galindo J, et al. Survival of Mexican children with acute lymphoblastic leukaemia under treatment with the protocol from the Dana-Farber Cancer Institute 00-01. *Biomed Res Int*. 2015;2015:576950.
2. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med*. 2006;354:166–178.
3. Roberts KG, Mullighan CG. Genomics in acute lymphoblastic leukaemia: insights and treatment implications. *Nat Rev Clin Oncol*. 2015;12:344–357.
4. Borthakur G, O'Brien S. Pharmacology and clinical potential of oblimersen sodium in the treatment of chronic lymphocytic leukemia. *Blood Lymphat Cancer*. 2012;2:137–143.
5. Advani AS. New immune strategies for the treatment of acute lymphoblastic leukemia: antibodies and chimeric antigen receptors. *Hematology Am Soc Hematol Educ Program*. 2013;2013(1):131–137.
6. Nakanishi T, Song Y, He C, et al. Autophagy is associated with cucurbitacin D-induced apoptosis in human T cell leukemia cells. *Med Oncol*. 2016;33:1–8.
7. Wang Z, Xu F, Yuan N, et al. Rapamycin inhibits pre-B acute lymphoblastic leukemia cells by downregulating DNA and RNA polymerases. *Leuk Res*. 2014;38(8):940–947.
8. Zhang C, Ryu YK, Chen TZ, Hall CP, Webster DR, Kang MH. Synergistic activity of rapamycin and dexamethasone in vitro and in vivo in acute lymphoblastic leukemia via cell-cycle arrest and apoptosis. *Leuk Res*. 2012;36:342–349.
9. Pilátová M, Šarišský M, Kutschy P, et al. Cruciferous phytoalexins: antiproliferative effects in T-Jurkat leukemic cells. *Leuk Res*. 2005;29(4):415–421.
10. Lucas DM, Edwards RB, Lozanski G, et al. The novel plant-derived agent silvestrol has B-cell selective activity in chronic lymphocytic leukemia and acute lymphoblastic leukemia in vitro and in vivo. *Blood*. 2009;113(19):4656–4666.
11. Abdelwahab SI, Abdul AB, Mohan S, et al. Zerumbone induces apoptosis in T-acute lymphoblastic leukemia cells. *Leuk Res*. 2011;35(2):268–271.
12. Chuang WC, Ho YC, Liao JW, Lu FJ. Dunaliella salina exhibits an antileukemic immunity in a mouse model of WEHI3 leukemia cells. *J Agric Food Chem*. 2014;62:11479–11487.
13. Wu CF, Karioti A, Rohr D, Bilia AR, Efferth T. Production of rosmarinic acid and salvianolic acid B from callus culture of Salvia miltiorrhiza with cytotoxicity towards acute lymphoblastic leukemia cells. *Food Chem*. 2016;201:292–297.
14. Horie Y, Nemoto H, Itoh M, Kosaka H, Morita K. Fermented brown rice extract causes apoptotic death of human acute lymphoblastic leukemia cells via death receptor pathway. *Appl Biochem Biotechnol*. 2016;178(8):1–13.
15. Gautam LN, Ling T, Lang W, Rivas F. Anti-proliferative evaluation of monoterpene derivatives against leukemia. *Eur J Med Chem*. 2016;113:75–80.
16. De Ford C, Heidersdorf B, Haun F, et al. The clerodane diterpene casearin J induces apoptosis of T-ALL cells through SERCA inhibition, oxidative stress, and interference with notch1 signaling. *Cell Death Dis*. 2016;7(1):e2070.
17. Kachlany SC, Schwartz AB, Balashova NV, et al. Anti-leukemia activity of a bacterial toxin with natural specificity for LFA-1 on white blood cells. *Leuk Res*. 2010;34(6):777–785.
18. Haß C, Belz K, Schoeneberger H, Fulda S. Sensitization of acute lymphoblastic leukemia cells for LCL161-induced cell death by targeting redox homeostasis. *Biochem Pharmacol*. 2016;105:14–22.
19. Gerges S, Rohde K, Fulda S. Cotreatment with Smac mimetics and demethylating agents induces both apoptotic and necroptotic cell death pathways in acute lymphoblastic leukemia cells. *Cancer Lett*. 2016;375(1):127–132.
20. Feuser PE, Gaspar PC, Jacques AV, et al. Synthesis of ZnPc loaded poly(methyl methacrylate) nanoparticles via miniemulsion polymerization for photodynamic therapy in leukemic cells. *Mater Sci Eng C Mater Biol Appl*. 2016;60:458–466.
21. Taghdisi SM, Danesh NM, Lavaee P, et al. Double targeting, controlled release and reversible delivery of daunorubicin to cancer cells by polyvalent aptamers-modified gold nanoparticles. *Mater Sci Eng C Mater Biol Appl*. 2016;61:753–761.
22. Cao J, Li L, Chen C, et al. RNA interference-mediated silencing of NANOG leads to reduced proliferation and self-renewal, cell cycle arrest and apoptosis in T-cell acute lymphoblastic leukemia cells via the p53 signaling pathway. *Leuk Res*. 2013;37(9):1170–1177.
23. Stanciu-Herrera C, Morgan C, Herrera L. Anti-CD19 and anti-CD22 monoclonal antibodies increase the effectiveness of chemotherapy in Pre-B acute lymphoblastic leukemia cell lines. *Leuk Res*. 2008;32(4):625–632.
24. Kato J, Satake N, O'Donnell RT, Abuhay M, Lewis C, Tuscano JM. Efficacy of a CD22-targeted antibody-saporin conjugate in a xenograft model of precursor-B cell acute lymphoblastic leukemia. *Leuk Res*. 2013;37(1):83–88.
25. Qian L, Li D, Ma L, et al. The novel anti-CD19 chimeric antigen receptors with humanized scFv (single-chain variable fragment) trigger leukemia cell killing. *Cell Immunol*. Epub 2016 Mar 14.
26. Weeks RJ, Ludgate JL, LeMee G, Morison IM. TESTIN induces rapid death and suppresses proliferation in childhood b acute lymphoblastic leukaemia cells. *PLoS One*. 2016;11(3):e0151341.
27. Zhang FH, Ling YW, Zhai X, et al. The effect of imatinib therapy on the outcome of allogeneic stem cell transplantation in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Hematology*. 2013;18(3):151–157.
28. Ravandi F, O'Brien SM, Cortes JE, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome–positive acute lymphoblastic leukemia. *Cancer*. 2015;121(23):4158–4164.
29. Jabbour E, Kantarjian H, Ravandi F, et al. First report of a phase ii prospective study of combination of hyper-cvad with ponatinib in frontline therapy of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Lancet Oncol*. 2015;16(15):1547–1555.
30. Bargou R, Leo E, Zugmaier G, et al. Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. *Science*. 2008;321:974–977.

31. Topp MS, Goekbuget N, Zugmaier G, et al. Anti-CD19 BiTE blinatumomab induces high complete remission rate and prolongs overall survival in adult patients with relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL). *ASH Annu Meet Abstr*. 2012;120:670.
32. Thomas X. Profile of inotuzumab ozogamicin and its potential in the treatment of acute lymphoblastic leukemia. *Blood Lymphat Cancer*. 2014;2014:1–8.
33. Kantarjian HM, Lioure B, Kim SK, et al. A phase II study of coltuximab ravtansine (SAR3419) monotherapy in patients with relapsed or refractory acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk*. 2016;16(3):139–145.
34. Lissitchkov T, Arnaudov G, Peytchev D, Merkle K. Phase-I/II study to evaluate dose limiting toxicity, maximum tolerated dose, and tolerability of bendamustine HCl in pre-treated patients with B-chronic lymphocytic leukaemia (Binet stages B and C) requiring therapy. *J Cancer Res Clin Oncol*. 2005;132(2):99–104.
35. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. *J Clin Oncol*. 2009;27:4378–4384.
36. Forconi F. Three years of ibrutinib in CLL. *Blood*. 2015;125:2455–2456.
37. Hainsworth JD, Litchy S, Barton JH, et al. Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol*. 2003;21:1746–1751.
38. Jean GW, Comeau JM. Role of obinutuzumab in the treatment of chronic lymphocytic leukemia. *Am J Health Syst Pharm*. 2015;72:933–942.
39. Moreno C, Montillo M, Panayiotidis P, et al. Ofatumumab in poor-prognosis chronic lymphocytic leukemia: a Phase IV, non-interventional, observational study from the European Research Initiative on Chronic Lymphocytic Leukemia. *Haematologica*. 2015;100(4):511–516.
40. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014;370(11):997–1007.
41. Cerquozzi S, Owen C. Clinical role of obinutuzumab in the treatment of naive patients with chronic lymphocytic leukemia. *Biologics*. 2015;9:13–22.
42. Brown JR, O'Brien S, Kingsley CD, et al. Obinutuzumab plus fludarabine/cyclophosphamide or bendamustine in the initial therapy of CLL patients: the phase 1b GALTON trial. *Blood*. 2015;125:2779–2785.
43. Byrd JC, Kipps TJ, Flinn IW, et al. Phase 1/2 study of lumiliximab combined with fludarabine, cyclophosphamide, and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia. *Blood*. 2010;115(3):489–495.
44. Kipps TJ, Eradat H, Grosicki S, et al. A phase 2 study of the BH3 mimetic BCL2 inhibitor navitoclax (ABT-263) with or without rituximab, in previously untreated B-cell chronic lymphocytic leukemia. *Leuk Lymphoma*. 2015;12:1–8.
45. Brown JR, Tesar B, Yu L, et al. Obatoclax in combination with fludarabine and rituximab is well-tolerated and shows promising clinical activity in relapsed chronic lymphocytic leukemia. *Leuk Lymphoma*. 2015;18:1–7.