Review Article

iMedPub Journals
www.imedpub.com

Journal of Stem Cell Biology and Transplantation
ISSN 2575-7725

2018
Vol.2 No.1:1

DOI: 10.21767/2575-7725.100018

Hematopoietic Stem Cell Transplantation for Adult Acute Lymphoblastic Leukemia in the Era of Novel Agents and Targeted Therapies

Al-Anazi KA*

Department of Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital, Dammam, Saudi Arabia

***Corresponding author:** Al-Anazi KA

kaa_alanazi@yahoo.com

Department of Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital, P.O. Box: 15215, Dammam 31444, Saudi Arabia

Tel: +966 - 03- 8431111
Fax: +966 -13- 8427420

Abstract

The outcomes of adult patients with acute lymphoblastic leukemia have improved significantly due to the recent advances in diagnostics and in therapeutic interventions. The adoption of pediatric chemotherapeutic regimens in adolescents and young adults, the availability of several novel and targeted therapies, and the provision of safer modalities of stem cell transplants have yielded higher response rates and improved survival.

This review article will be a recent update on the role of hematopoietic stem cell transplantation in adults with acute lymphoblastic leukemia in the era of novel agents and targeted therapies. Various modalities of stem cell therapies in different subtypes of acute lymphoblastic leukemia in addition to various modalities of novel therapies will also be discussed thoroughly.

Keywords: Acute lymphoblastic leukemia; Hematopoietic stem cell transplantation; Risk stratification; Conditioning therapy; Immunotherapies; Monoclonal antibodies

Received: April 12, 2017; **Accepted:** April 25, 2017; **Published:** May 02, 2018

Citation: Al-Anazi KA (2018) Hematopoietic Stem Cell Transplantation for Adult Acute Lymphoblastic Leukemia in the Era of Novel Agents and Targeted Therapies. J. Stem Cell Biol. Transplant. Vol.2, No.1:1

Introduction

Acute lymphoblastic leukemia (ALL), a clonal expansion or malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood and extramedullary sites, is a highly heterogeneous disease comprising several entities that have distinct clinical manifestations, therapeutic strategies and prognostic implications [1,2].

Worldwide, different induction chemotherapeutic regimens are utilized in the treatment of adult patients with ALL [3-6]. However, the main constituents of these chemotherapeutic regimens are almost similar with different dosing and treatment schedules and they include: anthracyclines such as daunorubicin, doxorubicin or idarubicin; corticosteroids such as prednisolone or dexamethasone; vincristine; L-asparaginase; cyclophosphamide; 6-mercaptopurine; and intrathecal (IT), oral as well as intravenous (IV) methotrexate [3-7].

Recently, the more intensified pediatric ALL chemotherapeutic regimens have been adopted in adolescents and young adults (AYAs), 15-40 years of age, having ALL and their use has been associated with superior response rates compared with the traditional adult regimens of chemotherapy [3,5,8].

Genetics, prognosis and risk stratification in ALL

Cytogenetic abnormalities occur in up to 85% of ALL patients. Also, numerical chromosomal abnormalities, alone or in association with structural changes, occur in 50% of patients with ALL [2,9,10]. The most common chromosomal abnormalities that are encountered in patients with ALL include: (1) Philadelphia chromosome (t 9,22), (2) chromosomal abnormalities that are associated with higher risk of central nervous system involvement such as: t 4,11; t 8,14 and t 14q+, (3) chromosomal abnormalities that are associated with high white cell and blast cell counts at presentation and high risk of relapse such as: t 9,22 and t 4,11, and (4) other common cytogenetic abnormalities that are encountered in patients with ALL include: t 10,14; t 1,14; deletion 11q22; deletion 11q23; hypodiploidy and hyperdiploidy [2,9-12]. Examples of the main molecular abnormalities that occur in ALL patients include: BCR-ABL1, ATM, MLL, TCRα, TCRβ, HOX11, HOX11L2, CDKN2A, CDKN2B, TAL1, TAL2, C-MYC, CRLF2, IKZF1, JAK2, CASP8AP2, IgH/BCL11B, NUP214-ABL, miR15, miR16, TCF3-PBX1, E2A-HLF, ETV6-RUNX1, EBF1, RB1, CREBBP1, SETD2, FOXO3A, KMT2A (MLL), EPHA7, GRIK2, BLIMP1 and FYN [11-13].

Studies have shown that the factors associated with prognosis and risk stratification in patients with ALL include: (1) age, (2) white blood count (WBC) count at presentation and proportion of circulating blasts, (3) presence or absence of extramedullary disease, (4) immunophenotyping profile and ALL subtype, (5) cytogenetic abnormalities and genetic mutations, (6) molecular and gene expression profiles, (7) rapidity and degree of cytoreduction, and (8) presence or absence of measurable residual disease at any stage of treatment [13-16]. ALL patients are stratified into the following 4 risk groups according to their cytogenetic profiles and other risk factors such as: age, WBC count at presentation, response or resistance to induction therapy: (1) low-risk with favorable cytogenetics, (2) standard-risk (SR) with intermediate cytogenetic risk, (3) high-risk (HR) with HR cytogenetics and (4) very HR with very HR cytogenetics [16,17].

High risk features that predict poor long-term outcome even with intensive chemotherapy in patients with ALL include: (1) age >35 years, (2) WBC count at presentation >30,000 in B-lineage and >100,000 in T-lineage, (3) pro-B; early and mature T cell types, (4) CD 20 positivity and CD 10 negative pre-B ALL on immunophenotyping, (5) poor performance status, (6) poor response to prednisolone, (7) peripheral blood blasts ≥ 5% on day15, (8) failure to achieve remission >4 weeks of induction chemotherapy, (9) involvement of central nervous system, (10) clinical relapse, and (11) presence of MRD (minimal residual disease: detectable molecular and immunophenotypic evidence of disease whilst in morphologic remission), (12) HR cytogenetic and molecular abnormalities including: + 8, - 7, deletion 6q, low hypodiloidy, near triploidy, immunoglobulin H gene rearrangement, intrachromosomal amplification of chromosome 21; t 8,14; t 4,11; t 1,19; t 9,22; Philadelphia-like (Ph-like) ALL and complex cytogenetics, and (13) HR genetic mutations including: IKZF1 deletion, unmutated NOTCH1, MLL (mixed lineage leukemia gene rearrangement, 11q23), RAS-PTEN altered, JAK 2 mutation, KMT2A rearrangement, CREBBP, CRLF2,ETP, PBX-E2A+, and BAALC+ [2,18-24].

HSCT in Adults with ALL

GVL effect and MRD

Several studies in patients with ALL have shown: (1) high incidence of relapse following cytotoxic chemotherapy or even allogeneic hematopietic stem cell transplantation (HSCT) thus contributing to treatment failure, and (2) graft versus host disease (GVHD) encountered in the post-HSCT period has a protective effect against disease relapse by providing potent graft versus leukemia (GVL) effect [25-29]. Other studies have shown the prognostic relevance of detection of MRD in patients with ALL subjected to HSCT as MRD identified prior to allogeneic HSCT has been found to be the strongest predictor of post-HSCT relapse in ALL patients [30,31]. Evaluation or monitoring of MRD in ALL patients can be performed by: (1) flow cytometry, (2) real-time quantitative polymerase chain reaction, and (3) next generation sequencing [30,32].

Autologous HSCT in ALL

Complete remission (CR) can be achieved in approximately 80% of adults with ALL, but relapse occurs frequently leading to poor long-term disease-free survival (DFS) [33,34]. After achieving CR, patients with ALL can receive either consolidation followed by maintenance chemotherapy or allogeneic HSCT for HR patients or autologous HSCT for SR patients or HR patients who do not have an HLA identical sibling donor [34,35].

Autologous HSCT in patients with ALL was first introduced nearly 60 years ago [34]. Once performed in patients with ALL in CR1, autologous HSCT can produce leukemia-free survival in up to 65% of patients [34]. Autologous HSCT combined with post-transplantation maintenance therapy in the form of 6-mercaptopurine, methotrexate, vincristine and prednisolone or TKIs for Philadelphia chromosome (Ph+) ALL that could be valid therapeutic options in adult patients with ALL [35-37]. In patients with ALL, relapse rates can be reduced and outcomes can be improved by using adoptive immunotherapy and maintenance therapy after autologous HSCT [37,38]. Also, novel therapies such as blinatumomab may reduce the burden of MRD prior to autologous HSCT, thus making the combination of autologous HSCT and novel therapies a real alternative to allogeneic HSCT and prolonged maintenance therapy for ALL patients [36].

Conditioning therapies for allogeneic HSCT

Allogeneic HSCT cures hematologic malignancies by the pre-transplantation conditioning therapy that kills leukemic cells directly and graft versus tumor (GVT) effect [39]. Recently, the outcome of HSCT has been steadily improving due to improvements in: conditioning therapies, GVHD prophylaxis and therapy, supportive care facilities, new antimicrobial agents, advanced diagnostic tools, availability of novel agents and targeted therapies such as TKIs, and donor selection by improvement of human leukocyte antigen (HLA) typing methods and the increased utilization of matched unrelated donors (MUDs) [25,40,41].

For the last 40 years, the standard myeloablative conditioning (MAC) regimen for ALL has been the combination of total body irradiation (TBI) and IV cyclophosphamide [42,43]. Alternative MAC regimens, with comparable efficacy and favorable toxicity profiles, include various combinations of: etoposide, fractionated TBI, cyclophosphamide, busulfan, melphalan, treosulfan, fludarabine, anti-thymocyte globulin, clofarabine and cytosine arabinoside [39,41,44-48].

Reduced intensity conditioning (RIC) regimens, which provide relapse protection by means of GVL effect, have been used extensively in adults with hematologic malignancies including ALL [49,50]. RIC-allogeneic HSCT is indicated in the presence of: old age, poor performance status, concurrent infection, significant organ dysfunction, and comorbid medical conditions [49,50]. RIC regimens have been associated with acceptable rates of donor engraftment and lower rates of treatment related mortality in comparison with MAC regimens [50].

The new therapeutic strategies that have been adopted in adults with ALL include: various TKIs for Ph+ ALL, pediatric inspired chemotherapeutic regimens for Philadelphia chromosome negative (Ph-) ALL, and HLA-haploidentical HSCT [49]. However, these strategies should be selected based on: age of the patient, Philadelphia chromosome positivity, donor availability, disease risk stratification and safety as well as efficacy of the therapeutic intervention [49].

Allogeneic HSCT in ALL

ALL patients having HR features are less likely to respond well to chemotherapy and are more likely to relapse. Thus, in order to have optimal control of their leukemia, these patients may require more intensified chemotherapeutic regimens, novel therapies in addition to HSCT [2,37-40]. Indications of allogeneic HSCT in adults with ALL include: (1) Ph+ ALL in CR1, (2) ALL with Ph-like molecular signature, (3) HR or very HR ALL in CR1, (4) relapsed ALL (ALL in CR2 or beyond), (5) primary refractory disease (ALL refractory to induction or first-line chemotherapy), after achievement of CR following salvage therapy, (6) presence of MRD at any stage during the course of the disease, regardless their initial risk group (SR or HR), and (7) MLL (mixed lineage leukemia) gene rearrangement [51-62].

In adult patients with ALL, post-remission therapies include: consolidation chemotherapy followed by maintenance therapy and autologous or allogeneic HSCT [60,61]. The role of frontline allogeneic HSCT for patients with ALL in CR1 is still controversial [63]. However, three meta-analyses that included 41 studies showed potential benefit of allogeneic HSCT in CR1 and they came to the following conclusions: (1) compared to chemotherapy alone or chemotherapy followed by autologous HSCT, myeloablative matched sibling donor (MSD) allografts had absolute survival benefit of up to 15% at 5 years, (2) MSD allografts improve survival in patients <35 years of age and constitute the optimal post-remission therapy in ALL patients ≥ 15 years old, (3) compared to chemotherapy, there was no beneficial effect of autologous HSCT, and (4) MSD allografts not only offered superior overall survival (OS) and DFS but also reduced the risk of relapse significantly although they were associated with increased risk of non-relapse mortality (NRM) [61,62,64].

In adults with ALL who are eligible for HSCT, either MAC therapies or RIC regimens can be offered according to the age and comorbid medical conditions of the recipient [47,65,66]. Also, the following stem cell sources can be utilized in recipients of allogeneic HSCT: MSD, MUD and umbilical cord blood (UCB) [23,65,67].

Focus on haploidentical HSCT

Haploidentical HSCT evolved several decades ago and over the years it has undergone several modifications in order to improve the: conditioning therapy, graft manipulation as well as post-transplantation immunosuppression [56,57,68]. Techniques that have been used to improve the outcome of this form of HSCT include: CD3/CD19 depletion so as to reduce GVHD; KIR B haplotype donors to lower relapse rates due to GVL effect; and infusion of high numbers of CD34+ cells in order to improve immune reconstitution [69]. Recently, unmanipulated allografts and post-transplantation cyclophosphamide yielded excellent outcomes that are comparable to those of unrelated UCB transplantation and MUD allografts [65,66,70].

In patients with Ph-ALL in CR1, haploidentical HSCT represents a valuable alternative for patients who lack MSDs [71,72]. Also, in adults with HR-ALL in CR1, haploidentical HSCT performed with post-transplantation cyclophosphamide has produced 52% DFS at 3 years, thus providing a suitable alternative to HLA-matched HSCT [63].

HSCT in T-cell ALL

T-cell ALL, which is common in adolescents and older patients, is an aggressive neoplasm derived from malignant transformation of lymphoblasts committed to T-cell lineage. Compared to B-cell ALL, it carries poorer prognosis due to: (1) more extensive involvement of bone marrow and extramedullary sites, (2) higher relapse rates even after allogeneic HSCT, and (3) higher incidence of drug resistance which is attributed to aberrant signaling pathways [73-78].

In the treatment of T-cell ALL, there is synergism between JAK 3 inhibitors and MEK/BCL2 inhibitors [76]. Allogeneic HSCT is a potentially curative therapeutic option for patients with T-cell ALL, but its use has been associated with high rates of relapse thus contributing to treatment failure [75]. Nelarabine which has selective cytotoxicity against T-cell lymphoblasts is usually used in relapsed and refractory T-cell ALL [73,79]. It is indicated in treating relapses post-allogeneic HSCT and in maintenance therapy following transplantation in HR patients [79]. In patients with T-cell ALL relapsing after allogeneic HSCT, the combination of nelarabine and donor lymphocyte infusions (DLIs) may provide long-term disease control and survival [77].

HSCT in Ph+ ALL

Philadelphia chromosome positivity is the commonest recurrent cytogenetic abnormality observed in adults with ALL as it has been reported in up to 25% of patients [80-84]. The introduction of TKIs into the therapeutic regimens of Ph+ ALL has been the most significant therapeutic advancement in recent years [81].

In adolescents with Ph+ALL, allogeneic HSCT is a controversial issue and there is increasing reluctance to offer allogeneic HSCT to this group of patients in the era of TKIs [80,84,85]. Studies have shown that in adolescents with Ph+ALL: excellent outcomes of the combination of TKI and chemotherapy with OS of 88% at 3 years, achievement of complete hematological remission in approximately 95% of patients, and no advantage of subjecting patients to allogeneic HSCT [86,87]. In young adults with Ph+ ALL studies have shown that: results of allogeneic HSCT are superior to chemotherapy alone; MSD and MUD allografts have yielded equivalent outcomes; in patients subjected to allogeneic HSCT: age, WBC count at presentation and early response to treatment have been found to be independent prognostic indicators; and advantage of early performance of allogeneic HSCT once morphologic remission is achieved [88-91].

The choice of TKI in the treatment of Ph+ALL is influenced by: toxicity profile, administration schedule, comorbid medical conditions, cost and patient preference [5]. Allogeneic HSCT is a potentially curative therapeutic modality, but it requires availability of a healthy HLA matching donor and it is associated with high rates of relapse and NRM [68]. However, haploidentical allogeneic HSCT is an alternative option for patients with Ph+ ALL who lack an HLA matching donor and its use is associated with lower relapse rate [92].

Philadelphia-like ALL

Ph-like ALL was adopted as a provisional entity in the recent world health organization classification [93]. It shares a similar gene expression profile with Ph+ ALL but lacks the BCR-ABL fusion or the t 9,22 by routine cytogenetics, FISH or molecular analysis [94,95]. Ph-like ALL occurs in up to 25% of adolescents and young adults with B-cell ALL and it is associated with: (1) deletion mutation involving IKZF1 gene that codes for the transcription factor IKAROS, (2) resistance to chemotherapy, and (3) poorer prognosis compared to other pre-B ALL subtypes [95].

Examples of molecular targets in Ph-like ALL include: ABL1, ABL2, CSF1R1, PDGFRB, EPOR, JAK2, CRLF2, JAK1, JAK3, FLT3, IL2RB, IL7R, TYK2, SH2B3, NRAS, KRAS, NF1, PTPN1, NTRK3 and PTK2B [96-101]. Examples of the targeted therapies that are currently used in the treatment of Ph-like ALL are: imatinib, dasatinib, nilotinib, poatinib, JAK2 inhibitors, JAK1 inhibitors, JAK3 inhibitors, FLT3 inhibitors, TYK 2 inhibitors, crizotinib and FAK inhibitors [96-101]. Examples of the investigational targeted therapies that can be used in the future treatment of Ph-like ALL include: givinostat, JQ1, luminespib and selumetinib targeting CRLF2; rapamycin that targets m-TOR activated pathway; gedatolisib targeting PI3K and m-TOR activated pathway; and birinapant which targets tumor necrosis factor-α-dependent pathway [93,102].

Relapse of ALL before and after HSCT

Despite receiving the standard chemotherapeutic regimens, up to 25% of ALL patients experience relapses of their disease at 5 years from diagnosis and initial therapy [103,104]. However, the prognosis of patients with relapsed ALL is poor as only a minority of adults with ALL who relapse after first line therapy can be rescued [103-105]. Salvage chemotherapeutic regimens in patients with relapsed ALL include: mitoxantrone, etoposide and cytarabine and the combination of fludarabine, cytarabine, pegylated-asparaginase and granulocyte colony stimulating factor [105]. Unfortunately, salvage chemotherapy alone is not curative in the setting of relapsed ALL [104]. However, allogeneic HSCT offers the best and may be the only chance for cure in adult patients with relapsed ALL [103-105]. GVHD, MRD, intrinsic factors of the disease and transplantation characteristics affect the occurrence as well as the outcome of ALL relapse after HSCT [106]. Unfortunately, the prognosis of patients with ALL who relapse after HSCT and those who are refractory to chemotherapy is extremely poor with < 10% long-term survival [23,78,107].

Management of ALL relapse post-HSCT includes: tapering of immunosuppressive therapy; salvage chemotherapy followed by second allogeneic HSCT; pre-emptive immunotherapy in the form of DLI with frequent MRD monitoring; post-transplantation maintenance therapy; the use of novel and targeted therapies in post-HSCT to prevent further relapses; and enrollment in clinical trials [106-108].

Novel and targeted therapies in ALL

ALL is a malignancy that has genetic basis and it is influenced by epigenetics [109,110]. Examples of the main molecular markers and the important genetic targets in ALL include: BCR-ABL1; BCR-ABL1-like; ETV6-RUNX1; IKZF1; CDKN2A; CDKN2B and NOTCH1 [109]. Examples of the novel agents and targeted therapies that are currently used or under development are included in **Table 1** [1,2,51,54,109,111-116].

TKIs

The introduction of TKIs has revolutionized the therapy of patients with Ph+ ALL [81,90]. In patients with Ph+ ALL, the incorporation of TKIs into the treatment regimens at various stages of the disease has significantly improved the outcomes of patients. Imatinib, dasatinib and nilotinib have been incorporated in: the induction phase in combination with cytotoxic chemotherapy, in the consolidation and maintenance phases in conjunction with cytotoxic chemotherapy in patients who are not candidates for allogeneic HSCT, and in the post-transplantation maintenance therapy in recipients of allogeneic HSCT [80,117-120].

Ponatinib, a pan-bcr/abl TKI, is capable of inhibiting T315I kinase domain mutation that confers resistance to other TKIs and dismal prognosis [82,121]. It can be given prior to HSCT as bridging therapy to control disease and following HSCT to prevent disease relapse [82,122,123].

Nelarabine

Nelarabine, a purine nucleoside analogue and a soluble prodrug of Ara-G with specific cytotoxicity against T-lymphocytes, has significant activity in patients with T-cell ALL [124-132]. It is recommended for the treatment of adult patients with T-cell ALL who are in relapse or refractory to at least 2 chemotherapeutic regimens [124-131]. Its use in the treatment of patients having T-cell ALL relapsing after allogeneic HSCT has been associated with 90% OS at one year [130].

Blinatumomab

Blinatumomab, a bispecific T-cell engager monoclonal antibody construct, is designed to direct cytotoxic T-cells to CD19-expressing B-cells [133,134]. It is indicated in the treatment of patients with: Ph- relapsed/refractory pre-B ALL, pre-B ALL relapsing post-allogeneic HSCT, and HR Ph+ ALL [133,134]. The adverse effects of blimatumomab include: fever, neutropenia, neurotoxicity and cytokine release syndrome (CRS) [126].

CAR T-cells

Chimeric antigen receptors (CAR) consist of an extracellular antigen recognition domain linked to an intracellular signaling

domain [135,136]. T-cells of the patient may be genetically modified to express an artificial T-cell receptor termed CAR designed to be specific to a tumor associated antigen [137]. The most extensively investigated CAR in clinical setting targets CD19 which is expressed in most B-cell malignancies as well as on normal B-cells, so CAR-mediated destruction of normal B-cells may cause B-cell aplasia [135].

CAR T-cell therapy involves several laboratory, technical and clinical procedures that include: obtaining peripheral blood mononuclear cells by leukapheresis, CD3 (T-cell) separation, engineering of T-cells to express CAR, lymphodepletion, CAR T-cell infusion, and finally cell death or apoptosis of CD19+ lymphoblasts [135-138]. Indication for CAR T-cell therapy include: relapsed and refractory B-cell ALL, B-cell lymphoid malignancies as well as other types of malignant hematological diseases, in addition to treatment of relapse post-allogeneic HSCT [135,139,140].

Studies have shown that treatment options in relapse after allogeneic HSCT for lymphoid malignancies including ALL include: DLI, salvage chemotherapy followed by a second allogeneic HSCT, and CAR T-cell infusions, [135,139,140].

CAR T-cells have been shown to be effective in treating in patients with relapsed/refractory ALL even among patients who have failed to respond to allogeneic HSCT [141]. Durable remissions lasting for 20-24 months or even longer have been achieved [142,143]. Patients with low disease burden have experienced lower incidence of adverse effects including CRS and neurotoxicity than patients with higher disease burden [143]. Second generation CD19-directed CAR T-cells have shown promising results in treating B-cell ALL [144]. Although the traditional doses of CAR T-cells infused range between 2×10^5 and 2×10^7/kg, trials using doses as low as 1×10^5 have been shown to be safe and effective in the treatment of relapsed/refractory B-cell ALL [144]. The 4 initial clinical trials on the use of CAR T-cells in the treatment of R/R ALL in the United States included 71 patients. Retrovirus or lentivirus transduction or sleeping beauty trasposon electroporation was used. Either no conditioning therapy or conditioning with cyclophosphamide was given. The incidence of CRS was about 27% and CR rate was approximately 88% [135,138].

Adverse effects or complications of CAR T-cell therapy in relapsed and refractory ALL include: CRS, neurotoxicity, macrophage activation syndrome, aplasia of normal B-lymphocytes, and death [111,112,145-150]. Management of CRS includes: supportive care, corticosteroids, vasopressors, ventilatory support and anti-interleukin-6 receptor antibody (tocilizumab) therapy [150]. Novel and targeted therapies that can be used in the treatment of patients with ALL are shown in **Table 1** [1,2,54,109,111-116].

Precision medicine and drug repurposing

Recently, knowledge concerning ALL has advanced to the extent that precision medicine may become a reality in the near future [116]. The following have attributed to the adaptation of precision medicine: better understanding of the biology of the disease, risk stratification and obtaining important information by using advanced technology such as molecular assays, next generation sequencing, epigenetic tests and gene expression profiling [109,147,148,151]. Drug repurposing or repositioning is a potential alternative to new drug discovery that takes plenty of time, cost and effort [152,153]. Drugs that have

Table 1 Novel agents and targeted therapies that are either currently used or under development for the treatment of acute lymphoblastic leukemia.

1.	**Monoclonal antibodies, CD marker and conjugated CD marker antibodies**	Rituximab, Obintuzumab, Ofatumomab, Epratuzumab, Inotuzumab Ozogamicin, Gemtuzumab Ozogamicin, Moxetumomab Pasudodotox, Coltuximan Ravtansine (Sar3419), Denintuzumab Mefodotin (Gn-Cd19a), Adc-402, Combotox (Anti- Cd19 And Anti- Cd22) And Blinatumomab (Anti- Cd3; Cd 19 Construct)
2.	**FLT3 inhibitors**	Lestaurtinib, Midostaurin, Sunitinib and Tandutinib
3.	**Tyrosine kinase inhibitors (TKIs) and spleen TKIs**	Imatinib, Dasatinib and Nilotinib
4.	**Multikinase inhibitors**	Sorafinib
5.	**Proteasome inhibitors**	Bortezomib
6.	**JAK and TAM tyrosine kinase inhibitors**	Ruxolitinib
7.	**Hypomethylating agents or DNA methyltransferase inhibitors**	Dectitabine and Azacytidine
8.	**Histone deacetylase inhibitors**	Vorinostat, Lbh 589 and Pdx 101
9.	**PI3K-mTOR inhibitors**	Rad001, Nvp-Bez235, Nct01756118 and Rapamycin
10.	**Aurora inhibitors**	Mln 8237
11.	**BCL2 antagonists**	Obatoclax
12.	**Farnesyl transferase inhibitors**	-
13.	**Trail receptor antagonists**	-
14.	**Survivin inhibitors**	-
15.	**Microtubule, destabilizing agents**	ENMD-1198
16.	**Antifolates**	Pemetrexed
17.	**Heat shock protein inhibitors**	-
18.	**Chimeric antigen receptor T-cells (CAR T-cells)**	-
19.	**Nucleoside analogues**	Nelarabine, Clofarabine and Forodesine
20.	**Liposomal and pegylated compounds**	Liposomal or Sphingosomal Vincristine, Liposomal Doxorubicin, Liposomal Cytarabine, Pegylated Asparaginase and Liposomal Annamycin

been repositioned for the treatment of ALL include: dasatinib, niclosamide, telmisartan, nelfinavir, triptolide, neprilisin and artesunate (ART 838) [153-158].

Conclusions and Future Directions

The recent advances in the diagnostics mainly in cytogenetic and molecular assays as well as genomic and epigenetic techniques have led to tremendous progress in: knowledge of the biology of ALL, the diagnosis and classification of ALL, risk stratification, prognosis, development of novel and targeted therapies, monitoring of response to treatment in addition to the introduction of precision medicine. The recent improvements in the management of patients with ALL are attributed to several reasons including: improvements in our understanding of the biology of the disease; advancements in the diagnostic techniques; improvements in supportive care; adoption of dose-intense pediatric-inspired chemotherapeutic regimens in AYAs; progress in HSCT procedures; monitoring of MRD; and the availability of several novel agents, targeted therapies as well as cellular and immunotherapies.

Prior to the introduction of targeted therapies such as TKIs, certain ALL subtypes were associated with poor outcome. With the recent availability of several novel therapies, some aggressive ALL subtypes are potentially curable even without HSCT. The incorporation of novel therapies at various stages in the therapeutic paradigm of ALL will further improve the outcome of patients. So, the availability of the modern therapeutic interventions has translated into improved response rates and outcomes. The integration of novel and targeted therapies before and after transplantation has further improved the outcomes of patients with ALL. Nevertheless, the different therapeutic interventions that are available for adults with ALL should be considered complementary to each other.

Despite the use of the intensified pediatric chemotherapeutic regimens, the outcome of ALL is poorer in adults than in children particularly in patients with HR features or disease relapse. Thus, allogeneic HSCT has more indications in adults than in children. However, sequencing of therapies and the incorporation of other therapeutic interventions into the management of ALL, before and after transplantation, is likely to improve the outcome of patients further.

References

1 Terwilliger T, Abdul-Hay M (2017) Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer J 7: e577.

2 Faderl S, O'Brien S, Pui CH, Stock W, Wetzler M, et al. (2010) Adult acute lymphoblastic leukemia: concepts and strategies. Cancer 116: 1165-1176.

3 Ribera JM, Ribera J, Genesca E (2014) Treatment of adolescent and young adults with acute lymphoblastic leukemia. Mediterr J Hematol Infect Dis 6: e2014052.

4 De Angelo DJ (2005) The treatment of adolescents and young adults with acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program, pp: 123-130.

5 Larson RA (2017) Induction therapy for Philadelphia chromosome negative acute lymphoblastic leukemia in adults. Up to Date.

6 Spiekerman K (2016) Therapeutic management of acute lymphoblastic leukemia. Handbook of acute leukemia, pp: 65-76.

7 Rowe JM, Buck G, Burnett AK, Chopra R, Wiernik PH, et al. (2005) Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood 106: 3760-3767.

8 Nachman JB, La MK, Hunger SP, Heerema NA, Gaynon PS, et al. (2009) Young adults with acute lymphoblastic leukemia have an excellent outcome with chemotherapy alone and benefit from intensive post induction treatment: a report from the Children's Oncology Group. J Clin Oncol 27: 5189-5194.

9 Moorman AV, Harrison CJ, Buck GA, Richards SM, Secker-Walker LM, et al. (2007) Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood 109: 3189-3197.

10 Mrozek K, Harper DP, Aplan PD (2009) Cytogenetics and molecular genetics of acute lymphoblastic leukemia. Hematol Oncol Clin North Am 23: 991-1010.

11 Juarez-Velazquez MR, Salas-Labadia C, Reyes-Leon A, Navarrete-Meneses MP, Fuentes-Panana EM (2013) Genetic markers in the prognosis of childhood acute lymphoblastic leukemia. In:Clinical epidemiology of acute lymphoblastic leukemia. In Tech, pp: 193-235.

12 Forero-Castro M, Robledo C, Benito R, Abaigar M, Africa Martin A et al. (2016) Genome-wide DNA copy number analysis of acute lymphoblastic leukemia identifies new genetic markers associated with clinical outcome. PLoS One 11: e0148972.

13 Forero RM, Hernandez M, Hernandez- Rivas JM (2013) Genetics of acute lymphoblastic leukemia. In: Leukemia. In Tech, pp: 1-37.

14 Schultz KR, Pullen DJ, Sather HN, Shuster JJ, Devidas M, et al. (2007) Risk-and response-based classification of childhood B-precursor acute lymphoblastic leukemia: A combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). Blood 109: 926–935.

15 Marinescu C, Vladareanu AM, Mihai F (2015) Acute lymphocytic leukemia in adults. Pathologic features and prognosis. Rom J Intern Med 53: 31-36.

16 Horton TM, Steuber P (2017) Risk group stratification and prognosis for acute lymphoblastic leukemia in children and adolescents. Up To Date.

17 Chiaretti S, Zini G, Bassan R (2014) Diagnosis and subclassification of acute lymphoblastic leukemia. Mediterr J Hematol Infect Dis 6: e2014073.

18 Inaba H1, Greaves M, Mullighan CG (2013) Acute lymphoblastic leukaemia. Lancet 381: 1943-1955.

19 Khaled SK, Thomas SH, Forman SJ (2012) Allogeneic hematopoietic cell transplantation for acute lymphoblastic leukemia in adults. Curr Opin Oncol 24: 182-190.

20 Lussana F, Rambaldi A (2014) Role of allogeneic hematopoietic stem cell transplantation in adult patients with acute lymphoblastic leukemia. Mediterr J Hematol Infect Dis 6: e2014065.

21 Fagioli F, Quarello P, Zecca M, Lanino E, Rognoni C, et al. (2013) Hematopoietic stem cell transplantation for children with high-risk acute lymphoblastic leukemia in first complete remission: a report from the AIEOP registry. Haematologica 98: 1273-1381.

22 Russell LJ, Enshaei A, Jones L, Erhorn A, Masic D, et al. (2014) IGH @ translocations are prevalent in teenagers and young adults with acute lymphoblastic leukemia and are associated with a poor outcome. J Clin Oncol 32(14): 1453-1462.

23 Toft N, Birgens H, Abrahamsson J, Griskevicius L, Hallbook H, et al. (2018) Results of NOPHO ALL2008 treatment for patients aged 1-45 years with acute lymphoblastic leukemia. Leukemia 32: 606-615.

24 Sakura T, Hayakawa F, Sugiura I, Murayama T, Imai K, et al. (2018) High-dose methotrexate therapy significantly improved survival of adult acute lymphoblastic leukemia: a phase III study by JALSG. Leukemia 32: 626-632.

25 Lee S, Cho BS, Kim SY, Choi SM, Lee DG, et al. (2007) Allogeneic stem cell transplantation in first complete remission enhances graft-versus-leukemia effect in adults with acute lymphoblastic leukemia: antileukemic activity of chronic graft-versus-host disease. Biol Blood Marrow Transplant 13: 1083-1094.

26 Nordlander A, Mattsson J, Ringden O, Leblanc K, Gustafsson B, et al. (2004) Graft-versus-host disease is associated with a lower relapse incidence after hematopoietic stem cell transplantation in patients with acute lymphoblastic leukemia. Biol Blood Marrow Transplant 10: 195-203.

27 Bradfield SM, Radich JP, Loken MR (2004) Graft-versus-leukemia effect in acute lymphoblastic leukemia: the importance of tumor burden and early detection. Leukemia 18: 1156–1158.

28 Uzunel M, Mattsson J, Jaksch M, Remberger M, Ringden O (2001) The significance of graft versus host disease and pretransplantation minimal residual disease status to outcome after allogeneic stem cell transplantation in patients with acute lymphoblastic leukemia. Blood 98: 1982-1984.

29 Gassas A, Sung L, Saunders EF, Doyle J (2007) Graft-versus-leukemia effect in hematopoietic stem cell transplantation for pediatric acute lymphoblastic leukemia: significantly lower relapse rate in unrelated transplantations. Bone Marrow Transplant 40: 951-955.

30 van der Velden VH1, Panzer-Grumayer ER, Cazzaniga G, Flohr T, Sutton R, et al. (2007) Optimization of PCR-based minimal residual disease diagnostics for childhood acute lymphoblastic leukemia in a multi-center setting. Leukemia 21: 706-713.

31 Thakar MS, Talano J-A M, Tower RL, Kelly ME, Burke MJ (2014) Indications for transplantation in childhood acute leukemia and the impact of minimal residual disease on relapse: a review. Clin Pract 11: 79-90.

32 Bruggemann M1, Schrauder A, Raff T, Pfeifer H, Dworzak M, et al. (2010) Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18-20 September 2008. Leukemia 24: 521-535.

33 Dhedin N, Dombret H, Thomas X, Lheritier V, Boiron JM, et al. (2006) Autologous stem cell transplantation in adults with acute lymphoblastic leukemia in first complete remission: analysis of the LALA-85, -87 and -94 trials. Leukemia 20: 336-344.

34 Mato AR, Luger SM (2006) Autologous stem cell transplant in ALL: who should we be transplanting in first remission? Bone Marrow Transplant 37: 989-995.

35 Ding Z, Han MZ, Chen SL, Ma QL, Wei JL, et al. (2015) Outcomes of adults with acute lymphoblastic leukemia after autologous hematopoietic stem cell transplantation and the significance of pre transplantation minimal residual disease: analysis from a single center of China. Chin Med J 128: 2065-2071.

36 Mannis GN, Martin TG III, Damon LE, Andreadis C, Olin RL1, et al. (2016) Quantification of acute lymphoblastic leukemia clonotypes in leukapheresed peripheral blood progenitor cells predicts relapse risk after autologous hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 22: 1030-1036.

37 Sirohi B, Powles R, Treleaven J, Kulkarni S, Saso R, et al. (2008) The role of maintenance chemotherapy after auto transplantation for acute lymphoblastic leukemia in first remission: single-center experience of 100 patients. Bone Marrow Transplant 42: 105-112.

38 Zou D, Han M, Feng S, Li C, Qiu L, et al. (2000) Treatment of acute lymphoblastic leukemia by autologous stem cell transplantation: an analysis of 30 cases. Zhonghua Xue Ye Xue Za Zhi 21: 74-76.

39 Marks DI, Forman SJ, Blume KG, Perez WS, Weisdorf DJ, et al. (2006) A comparison of cyclophosphamide and total body irradiation with etoposide and total body irradiation as conditioning regimens for patients undergoing sibling allografting for acute lymphoblastic leukemia in first or second complete remission. Biol Blood Marrow Transplant 12: 438-453.

40 Doney K, Gooley TA, Deeg HJ, Flowers ME, Storb R, et al. (2011) Allogeneic hematopoietic cell transplantation with full-intensity conditioning for adult acute lymphoblastic leukemia: results from a single center, 1998-2006. Biol Blood Marrow Transplant 17: 1187-1195.

41 Gassas A, Sung L, Saunders EF, Doyle JJ (2006) Comparative outcome of hematopoietic stem cell transplantation for pediatric acute lymphoblastic leukemia following cyclophosphamide and total body irradiation or VP16 and total body irradiation conditioning regimens. Bone Marrow Transplant 38: 739-743.

42 Tracey J, Zhang M-J, Thiel E, Sobocinski KA, Eapen M (2013) Transplantation conditioning regimens and outcomes after allogeneic hematopoietic cell transplantation in children and adolescents with acute lymphoblastic leukemia. Biol Blood Marrow Transplant 19: 255-259.

43 Zohren F, Czibere A, Bruns I, Fenk R, Schroeder T, et al. (2009) Fludarabine, amsacrine, high-dose cytarabine and 12 Gy total body irradiation followed by allogeneic hematopoietic stem cell transplantation is effective in patients with relapsed or high-risk acute lymphoblastic leukemia. Bone Marrow Transplant 44: 785-792.

44 Daly A, Savoie ML, Geddes M, Chaudhry A, Stewart D, et al. (2012) Fludarabine, busulfan, antithymocyte globulin, and total body irradiation for pre transplantation conditioning in acute lymphoblastic leukemia: excellent outcomes in all but older patients with comorbidities. Biol Blood Marrow Transplant 18:1921-1926.

45 Kebriaei P, Madden T, Wang X, Thall PF, Ledesma C, et al. (2013) Intravenous BU plus Mel: an effective, chemotherapy-only transplant conditioning regimen in patients with ALL. Bone Marrow Transplant 48: 26-31.

46 Kroger N, Bornhauser M, Stelljes M, Pichlmeier U, Trenschel R, et al. (2015) Allogeneic stem cell transplantation after conditioning with

treosulfan, etoposide and cyclophosphamide for patients with ALL: a phase II-study on behalf of the German Cooperative Transplant Study Group and ALL Study Group (GMALL). Bone Marrow Transplant 50: 1503-1507.

47 Kebriaei P, Bassett R, Lyons G, Valdez B, Ledesma C, et al. (2017) Clofarabine plus busulfan is an effective conditioning regimen for allogeneic hematopoietic stem cell transplantation in patients with acute lymphoblastic leukemia: long-term study results. Biol Blood Marrow Transplant 23: 285-292.

48 Kebriaei P, Basset R, Ledesma C, Ciurea S, Parmar S, et al. (2012) Clofarabine combined with busulfan provides excellent disease control in adult patients with acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 18:1819-1826.

49 Imamura M, Shigematsu A (2015) Allogeneic hematopoietic stem cell transplantation in adult acute lymphoblastic leukemia: potential benefit of medium-dose etoposide conditioning. Exp Hematol Oncol 4: 20.

50 Verneris MR, Eapen M, Duerst R, Carpenter PA, Burke MJ, et al. (2010) Reduced-intensity conditioning regimens for allogeneic transplantation in children with acute lymphoblastic leukemia. Biol Blood Marrow Transplant 16: 1237-1244.

51 Hoelzer D, Bassan R, Dombret H, Fielding A, Ribera JM, et al. (2016) Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 27: v69-v82.

52 Larson RA (2017) General principles of hematopoietic cell transplantation for acute lymphoblastic leukemia in adults. Up To Date.

53 Ribera JM (2011) Allogeneic stem cell transplantation for adult acute lymphoblastic leukemia: when and how. Haematologica 96: 1083-1086.

54 Oyekunle A, Haferlach T, Kroger N, Klyuchnikov E, Zander AR, et al. (2011) Molecular diagnostics, targeted therapy, and the indication for allogeneic stem cell transplantation in acute lymphoblastic leukemia. Adv Hematol 154745.

55 Dhedin N, Huynh A, Maury S, Tabrizi R, Beldjord K, et al.; GRAALL group (2015) Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. Blood 125: 2486-2496.

56 Lazarus HM, Luger S (2007) Which patients with adult acute lymphoblastic leukemia should undergo a hematopoietic stem cell transplantation? Case-based discussion. Hematology Am Soc Hematol Educ Program, pp: 444-452.

57 Hochberg J, Khaled S, Forman SJ, Cairo MS (2013) Criteria for and outcomes of allogeneic haematopoietic stem cell transplant in children, adolescents and young adults with acute lymphoblastic leukaemia in first complete remission. Br J Haematol 161: 27-42.

58 El Fakih R, Kharfan-Dabaja MA, Aljurf M (2016) Refining the role of hematopoietic cell transplantation for acute lymphoblastic leukemia as novel therapies emerge. Biol Blood Marrow Transplant 22: 2126-2133.

59 Roth-Guepin G, Canaani J, Ruggeri A, Labopin M, Finke J, et al. (2017) Allogeneic stem cell transplantation in acute lymphoblastic leukemia patients older than 60 years: a survey from the acute leukemia working party of EBMT. Oncotarget 8: 112972–112979.

60 Li C-K (2010) Current indications of bone marrow transplantation (BMT) in pediatric malignant conditions; a review. Iran J Blood Cancer 2: 71-75.

61 Pidala J, Djulbegovic B, Anasetti C, Kharfan-Dabaja M, Kumar A (2011) Allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia (ALL) in first complete remission. Cochrane Database Syst Rev 5: CD008818.

62 Gupta V, Richards S, Rowe J (2013) Acute Leukemia Stem Cell Transplantation Trialists' Collaborative Group Allogeneic, but not autologous, hematopoietic cell transplantation improves survival only among younger adults with acute lymphoblastic leukemia in first remission: an individual patient data meta-analysis. Blood 121: 339-350.

63 Srour SA, Milton DR, Bashey A, Karduss-Urueta A, Al Malki MM, et al. (2017) Haploidentical transplantation with post-transplantation cyclophosphamide for high-risk acute lymphoblastic leukemia. Biol Blood Marrow Transplant 23: 318-324.

64 Messori A, Fadda V, Maratea D, Trippoli S (2013) Acute lymphoblastic leukemia in first complete remission: temporal trend of outcomes in studies comparing allogeneic transplant with autologous transplant or chemotherapy. Ann Hematol 92: 1221-1228.

65 Aversa F (2008) Haploidentical haematopoietic stem cell transplantation for acute leukaemia in adults: experience in Europe and the United States. Bone Marrow Transplant 41: 473-481.

66 Santoro N, Ruggeri A, Labopin M, Bacigalupo A, Ciceri F, et al. (2017) Unmanipulated haploidentical stem cell transplantation in adults with acute lymphoblastic leukemia: a study on behalf of the Acute Leukemia Working Party of the EBMT. J Hematol Oncol 10: 113.

67 Liu D, Huang X, Liu K, Xu L, Chen H, et al. (2008) Haploidentical hematopoietic stem cell transplantation without in vitro T cell depletion for treatment of hematological malignancies in children. Biol Blood Marrow Transplant 14: 469-477.

68 Rowe JM, Lazarus HM (2001) Genetically haploidentical stem cell transplantation for acute leukemia. Bone Marrow Transplant 27: 669-676.

69 Diaz MA, Perez-Martínez A, Herrero B, Deltoro N, Martinez I, et al. (2016) Prognostic factors and outcomes for pediatric patients receiving an haploidentical relative allogeneic transplant using CD3/CD19-depleted grafts. Bone Marrow Transplant 51: 1211-1216.

70 Ruggeri A, Labopin M, Sanz G, Piemontese S, Arcese W, et al. (2015) Comparison of outcomes after unrelated cord blood and un manipulated haploidentical stem cell transplantation in adults with acute leukemia. Leukemia 29:1891-1900.

71 Mo XD, Xu LP, Zhang XH, Liu DH, Wang Y, et al. (2015) Haploidentical hematopoietic stem cell transplantation in adults with Philadelphia-negative acute lymphoblastic leukemia: no difference in the high- and low-risk groups. Int J Cancer 136: 1697-1707.

72 Liu Q, Han L, Fan Z, Huang F, LI X, et al. (2016) Haploidentical hematopoietic stem cell transplant compared with matched sibling and unrelated transplants in adults with Philadelphia-negative acute lymphoblastic leukemia in first complete remission. Blood 128: 2299.

73 Bonifacio M, Perbellini O, Pizzolo G (2009) T-cell acute lymphoblastic lymphoma and T-cell lymphoblastic lymphoma: therapy in adults. Hematol Meeting Rep 3: 115-122

74 Burke MJ, Verneris MR, Le Rademacher J, He W, Abdel-Azim H, et al. (2015) Transplant outcomes for children with T cell acute lymphoblastic leukemia in second remission: a report from the Center for International Blood and Marrow Transplant Research. Biol Blood Marrow Transplant 21: 2154-2159.

75 Hamilton BK, Rybicki L, Abounader D, Adekola K, Advani A, et al. (2017) Allogeneic Hematopoietic cell transplantation for adult T cell acute lymphoblastic leukemia. Biol Blood Marrow Transplant 23: 1117–1121.

76 Degryse S, de Bock CE, Demeyer S, Govaerts I, Bornschein S, et al. (2018) Mutant JAK3 phosphoproteomic profiling predicts synergism between JAK3 inhibitors and MEK/BCL2 inhibitors for the treatment of T-cell acute lymphoblastic leukemia. Leukemia 32: 788-800.

77 Burley K, Wolf J, Raffoux E, Marks DI (2018) Long-term survival following post-allograft relapse of T-cell acute lymphoblastic leukaemia: a novel approach using nelarabine and donor lymphocyte infusions. Bone Marrow Transplant 53: 344-346.

78 Bongiovanni D, Saccomani V, Piovan E (2017) Aberrant signaling pathways in T-cell acute lymphoblastic leukemia. Int J Mol Sci 18: 1904.

79 Forcade E, Leguay T, Vey N, Baruchel A, Delaunay J, et al. (2013) Nelarabine for T cell acute lymphoblastic leukemia relapsing after allogeneic hematopoietic stem cell transplantation: an opportunity to improve survival. Biol Blood Marrow Transplant 19: 1124-1126.

80 Brissot E, Labopin M, Beckers MM, Socie G, Rambaldi A, Volin L, et al. (2015) Tyrosine kinase inhibitors improve long-term outcome of allogeneic hematopoietic stem cell transplantation for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia. Haematologica 100: 392-399.

81 Tanguy-Schmidt A, Rousselot P, Chalandon Y, Cayuela JM, Hayette S, et al. (2013) Long-term follow-up of the imatinib GRAAPH-2003 study in newly diagnosed patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: a GRAALL study. Biol Blood Marrow Transplant 19: 150-155.

82 Sora F, Chiusolo P, Laurenti L, Soverini S, Sica S, et al. (2016) Ponatinib before and after allogeneic stem cell transplantation for Ph+ acute lymphoblastic leukemia or lymphoid blast crisis of chronic myelogenous leukemia: a single center experience. J Bone Res 4: 169.

83 Stirewalt DL, Guthrie KA, Beppu L, Bryant EM, Doney K, et al. (2003) Predictors of relapse and overall survival in Philadelphia chromosome-positive acute lymphoblastic leukemia after transplantation. Biol Blood Marrow Transplant 9: 206-212.

84 Fielding AK (2011) Philadelphia-positive acute lymphoblastic leukemia--is bone marrow transplant still necessary? Biol Blood Marrow Transplant 17: S84-88.

85 Yanada M1, Naoe T (2006) Imatinib combined chemotherapy for Philadelphia chromosome-positive acute lymphoblastic leukemia: major challenges in current practice. Leuk Lymphoma 47: 1747-1753.

86 Schultz KR, Bowman WP, Aledo A, Slayton WB, Sather H, et al. (2009) Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol 27: 5175-5181.

87 Schultz KR, Carroll A, Heerema NA, Bowman WP, Aledo A, et al. (2014) Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia 28: 1467-1471.

88 Arico M, Schrappe M, Hunger SP, Carroll WL, Conter V, et al. (2010) Clinical outcome of children with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia treated between 1995 and 2005. J Clin Oncol 28: 4755-4761.

89 Fagioli F, Zecca M, Rognoni C, Lanino E, Balduzzi A, et al. (2012) Allogeneic hematopoietic stem cell transplantation for Philadelphia-positive acute lymphoblastic leukemia in children and adolescents: a retrospective multicenter study of the Italian Association of Pediatric Hematology and Oncology (AIEOP). Biol Blood Marrow Transplant 18: 852-860.

90 Kebriaei P, Saliba R, Rondon G, Chiattone A, Luthra R, et al. (2012) Long-term follow-up of allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: impact of tyrosine kinase inhibitors on treatment outcomes. Biol Blood Marrow Transplant 18: 584-592.

91 Byun YJ, Suh JK, Lee SW, Lee D, Kim H, et al. (2015) Favorable outcome of allogeneic hematopoietic stem cell transplantation followed by post-transplant treatment with imatinib in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood Res 50: 147-153.

92 Gao L, Zhang C, Gao L, Liu Y, Su Y, et al. (2015) Favorable outcome of haploidentical hematopoietic stem cell transplantation in Philadelphia chromosome-positive acute lymphoblastic leukemia: a multicenter study in Southwest China. Hematol Oncol 8: 90.

93 Wells J, Jain N, Konopleva M (2017) Philadelphia chromosome-like acute lymphoblastic leukemia: progress in a new cancer subtype. Clin Adv Hematol Oncol 15: 554-561.

94 Boer JM, den Boer ML (2017) BCR-ABL1-like acute lymphoblastic leukaemia: From bench to bedside. Eur J Cancer 82: 203-218.

95 Zhang Y, Le Beau MM (2017) cytogenetics and molecular genetics in acute lymphoblastic leukemia. Up To date.

96 Yokota T, Kanakura Y (2016) Genetic abnormalities associated with acute lymphoblastic leukemia. Cancer Sci 107: 721-725.

97 Lokhandwala PM, Ning Y (2016) Update on BCR-ABL1-like precursor B-cell acute lymphoblastic leukemia. Hematopathol 1: 11-15.

98 Reshmi RC, Harvey RC, Roberts KG, Stonerock E, Smith A, et al. (2017) Targetable kinase gene fusions in high risk B-ALL: a study from the Children's Oncology Group. Blood 129: 3352-3361.

99 Roberts KG, Gu Z, Payne-Turner D, McCastlain K, Harvey RC, et al. (2017) High frequency and poor outcome of Philadelphia chromosome-like acute lymphoblastic leukemia in adults. J Clin Oncol 35: 394-401.

100 Tasian SK, Hurtz C, Wertheim GB, Bailey NG, Lim MS, et al. (2017) High incidence of Philadelphia chromosome-like acute lymphoblastic leukemia in older adults with B-ALL. Leukemia 31: 981-984.

101 Roberts KG, Li Y, Payne-Turner D, Harvey RC, Yang YL, et al. (2014) Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med 371: 1005-1015.

102 Richmond J, Robbins A, Evans K, Beck D, Kurmasheva RT, et al. (2016) Acute sensitivity of Ph-like acute lymphoblastic leukemia to the SMAC-mimetic birinapant. Cancer Res 76: 4579-4591.

103 Lee EJ, Han JY, Lee JW, Jang PS, Chung NG, et al. (2012) Outcome of allogeneic hematopoietic stem cell transplantation for childhood acute lymphoblastic leukemia in second complete remission: a single institution study. Korean J Pediatr 55: 100-106.

104 Smith AR, Baker KS, Defor TE, Verneris MR, Wagner JE, et al. (2009) Hematopoietic cell transplantation for children with acute lymphoblastic leukemia in second complete remission: similar outcomes in recipients of unrelated marrow and umbilical cord

blood versus marrow from HLA matched sibling donors. Biol Blood Marrow Transplant 15: 1086-1093.

105 Kozlowski P, Astrom M, Ahlberg L, Bernell P, Hulegardh E, et al. (2012) High curability via intensive reinduction chemotherapy and stem cell transplantation in young adults with relapsed acute lymphoblastic leukemia in Sweden 2003-2007. Haematologica 97: 1414-1421.

106 Chen R, Campbell JL, Chen B (2015) Prophylaxis and treatment of acute lymphoblastic leukemia relapse after allogeneic hematopoietic stem cell transplantation. Onco Targets Ther 8: 405-412.

107 Poon LM, Hamdi A, Saliba R, Rondon G, Ledesma C, et al. (2013) Outcomes of adults with acute lymphoblastic leukemia relapsing after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 19: 1059-1064.

108 Willasch AM, Salzmann-Manrique E, Krenn T, Duerken M, Faber J, et al. (2017) Treatment of relapse after allogeneic stem cell transplantation in children and adolescents with ALL: the Frankfurt experience. Bone Marrow Transplant 52: 201-208.

109 Al-Anazi KA (2017) Molecular diagnostics moving hematological malignancies into the era of precision medicine. J Mol Genet Med 1: 1-5.

110 Mullighan CG (2016) Abstract IA02: Precision medicine in acute lymphoblastic leukemia. Clin Cancer Res 22: Abstract number IA02.

111 Maino E, Scattolin AM, Viero P, Sancetta R, Pascarella A (2015) Modern immunotherapy of adult B-lineage acute lymphoblastic leukemia with monoclonal antibodies and chimeric antigen receptor modified T cells. Mediterr J Hematol Infect Dis 7: e2015001.

112 Papadantonakis N, Advani AS (2016) Recent advances and novel treatment paradigms in acute lymphocytic leukemia. Ther Adv Hematol 7: 252-269.

113 De Angelo DJ (2015) The use of novel monoclonal antibodies in the treatment of acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2015: 400-405.

114 Daver N, O'Brien S (2013) Novel therapeutic strategies in adult acute lymphoblastic leukemia--a focus on emerging monoclonal antibodies. Curr Hematol Malig Rep 8: 123-131.

115 Lee-Sherick AB, Linger RM, Gore L, Keating AK, Graham DK (2010) Targeting paediatric acute lymphoblastic leukaemia: novel therapies currently in development. Br J Haematol 151: 295-311.

116 Hoelzer D (2011) Novel antibody-based therapies for acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2011: 243-249.

117 Mathisen MS, O'Brien S, Thomas D, Cortes J, Kantarjian H, et al. (2011) Role of tyrosine kinase inhibitors in the management of Philadelphia chromosome-positive acute lymphoblastic leukemia. Curr Hematol Malig Rep 6: 187-194.

118 Larson RA (2017) Post-remission therapy for Philadelphia chromosome positive acute lymphoblastic leukemia.in adults. Up To Date.

119 Jeha S, Coustan-Smith E, Pei D, Sandlund JT, Rubnitz JE, et al. (2014) Impact of tyrosine kinase inhibitors on minimal residual disease and outcome in childhood Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer 120: 1514-1519.

120 Manabe A, Kawasaki H, Shimada H, Kato I, Kodama Y, et al. (2015) Imatinib use immediately before stem cell transplantation in children with Philadelphia chromosome-positive acute lymphoblastic leukemia: Results from Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) Study Ph (+) ALL 04. Cancer Med 4: 682-689.

121 Leonard JT, Allen B, Slater S, Maziarz RT, Hayes-Lattin B (2017) A chemotherapy-free induction followed by allogeneic HSCT for Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL). Biol Blood Marrow Transplant 23: S287-S288.

122 Lupo-Stanghellini MT, Lunghi F, Assanelli AA, Guggiari E, Greco R, et al. (2016) Post-transplant treatment with ponatinib for patients with high-risk Philadelphia chromosome positive leukemia. Blood 128: 5810.

123 Nicolini FE, Basak GW, Kim DW, Olavarria E, Pinilla-Ibarz J, et al. (2017) Overall survival with ponatinib versus allogeneic stem cell transplantation in Philadelphia chromosome-positive leukemias with the T315I mutation. Cancer 123: 2875-2880.

124 Cooper TM (2007) Role of nelarabine in the treatment of T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma. Ther Clin Risk Manag 3: 1135-1141.

125 De Angelo DJ (2009) Nelarabine for the treatment of patients with relapsed or refractory T-cell acute lymphoblastic leukemia or lymphoblastic lymphoma. Hematol Oncol Clin North Am 23: 1121-1135.

126 Cohen MH, Johnson JR, Justice R, Pazdur R (2008) FDA drug approval summary: nelarabine (Arranon) for the treatment of T-cell lymphoblastic leukemia/lymphoma. Oncologist 3: 709-714.

127 Reilly KM, Kisor DF (2009) Profile of nelarabine: use in the treatment of T-cell acute lymphoblastic leukemia. Onco Targets Ther 2: 219-228.

128 DeAngelo DJ, Yu D, Johnson JL, Coutre SE, Stone RM, et al. (2007) Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. Blood 109: 5136-5142.

129 Gokbuget N, Basara N, Baurmann H, Beck J, Brüggemann M, et al. (2011) High single-drug activity of nelarabine in relapsed T-lymphoblastic leukemia/lymphoma offers curative option with subsequent stem cell transplantation. Blood 118: 3504-3511.

130 Kadia TM, Gandhi V (2017) Nelarabine in the treatment of pediatric and adult patients with T-cell acute lymphoblastic leukemia and lymphoma. Expert Rev Hematol 10: 1-8.

131 Roecker AM, Stockert A, Kisor DF (2010) Nelarabine in the treatment of refractory T-cell malignancies. Clin Med Insights Oncol 4: 133-141.

132 Winter SS, Dunsmore KP, Devidas M, Eisenberg N, Asselin BL, et al. (2015) Safe integration of nelarabine into intensive chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group Study AALL0434. Pediatr Blood Cancer 62: 1176-1183.

133 Khan MW, Gul Z (2016) Blinatumomab may induce graft versus host leukemia in patients with pre-B ALL relapsing after hematopoietic stem cell transplant. Clin Case Rep 4: 743-746.

134 Martinelli G, Boissel N, Chevallier P, Ottmann O, Gokbuget N, et al. (2017) 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 35: 1795-1802.

135 Pegram HJ, Smith EL, Rafiq S, Brentjens RJ (2015) CAR therapy for hematological cancers: can success seen in the treatment of B-cell acute lymphoblastic leukemia be applied to other hematological malignancies? Immunotherapy 7: 545-561.

136 Wang Z, Wu Z, Liu Y, Han W (2017) New development in CAR-T cell therapy. J Hematol Oncol 10: 53.

137 Brentjens RJ, Davila ML, Riviere I, Park J, Wang X, et al. (2013) CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. Sci Transl Med 5: 177ra38.

138 Davila ML, Brentjens RJ (2016) CD19-Targeted CAR T cells as novel cancer immunotherapy for relapsed or refractory B-cell acute lymphoblastic leukemia. Clin Adv Hematol Oncol 14: 802-808.

139 Zhu YM, Wu Z, Tan YP, Du YY, Liu Z, et al. (2016) Anti-CD19 chimeric antigen receptor T-cell therapy for adult Philadelphia chromosome-positive acute lymphoblastic leukemia: Two case reports. Medicine (Baltimore) 95: e5676.

140 Liu J, Zhong JF, Zhang X, Zhang C (2017) Allogeneic CD19-CAR-T cell infusion after allogeneic hematopoietic stem cell transplantation in B cell malignancies. J Hematol Oncol 10: 35.

141 Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, et al. (2014) Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 371: 1507-1517.

142 Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, et al. (2018) Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 378: 439-448.

143 Park JH, Riviere I, Gonen M, Wang X, Senechal B, et al. (2018) Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med 378: 449-459.

144 Pan J, Yang JF, Deng BP, Zhao XJ, Zhang X, et al. (2017) High efficacy and safety of low-dose CD19-directed CAR-T cell therapy in 51 refractory or relapsed B acute lymphoblastic leukemia patients. Leukemia 31: 2587-2593.

145 Davila ML, Riviere I, Wang X, Bartido S, Park J, et al. (2014) Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med 6: 224ra25.

146 Teachey DT, Lacey SF, Shaw PA, Melenhorst JJ, Maude SL, et al. (2016) Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Cancer Discov 6: 664-679.

147 Tasian SK, Gardner RA (2015) CD19-redirected chimeric antigen receptor-modified T cells: a promising immunotherapy for children and adults with B-cell acute lymphoblastic leukemia (ALL). Ther Adv Hematol 6: 228-2241.

148 Tang XY, Sun Y, Zhang A, Hu GL, Cao W, et al. (2016) Third-generation CD28/4-1BB chimeric antigen receptor T cells for chemotherapy relapsed or refractory acute lymphoblastic leukaemia: a non-randomised, open-label phase I trial protocol. BMJ Open 6: e013904.

149 Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, et al. (2016) CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest 126: 2123-2138.

150 Jackson HJ, Rafiq S, Brentjens RJ (2016) Driving CAR T-cells forward. Nat Rev Clin Oncol 13: 370–383.

151 Izraeli S, Shochat C, Tal N, Geron I (2014) Towards precision medicine in childhood leukemia--insights from mutationally activated cytokine receptor pathways in acute lymphoblastic leukemia. Cancer Lett 352: 15-20.

152 Wu H, Huang J, Zhong Y, Huang Q (2017) DrugSig: A resource for computational drug repositioning utilizing gene expression signatures. PLoS One 12: e0177743.

153 Sukhai MA, Spagnuolo PA, Weir S, Kasper J, Patton L, et al. (2011) New sources of drugs for hematologic malignancies. Blood 117: 6747-6755.

154 Hamdoun S, Jung P, Efferth T (2017) Drug repurposing of the anthelmintic niclosamide to treat multidrug-resistant leukemia. Front Pharmacol 8: 110.

155 Zhao H, Shi P, Deng M, Jiang Z, Li Y, et al. (2016) Low dose triptolide reverses chemoresistance in adult acute lymphoblastic leukemia cells via reactive oxygen species generation and DNA damage response disruption. Oncotarget 7: 85515-85528.

156 Ye X-Y, Ling Q-Z, Chen S-J (2017) Identification of neprilysin as a potential target of arteannuin using computational drug repositioning. Braz J Pharm Sci 53: e16087.

157 Fox JM, Moynihan JR, Posner GH, Brown P, Civin CI, et al. (2014) Repurposing artemisinin's for treatment of acute leukemia. Cancer Res 74: Abstract number 818.

158 Meier-Stephenson V, Riemer J, Narendran A (2017) The HIV protease inhibitor, nelfinavir, as a novel therapeutic approach for the treatment of refractory pediatric leukemia. Onco Targets Ther 10: 2581-2593.