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Chapter 8

Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia in the Era of Novel Therapies

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http://dx.doi.org/10.5772/intechopen.73562

Abstract

Recently, the outcomes of patients with acute lymphoblastic leukemia have improved significantly due to the progresses achieved in diagnostics and various therapeutic interventions. In particular, the availability of several novel agents and targeted therapies as well as the provision of safer modalities of stem cell transplants have yielded higher responses and improved survival rates. The role of hematopoietic stem cell transplantation is reviewed in children and adults with acute lymphoblastic leukemia in the era of novel agents and targeted therapies. Various modalities of stem cell therapies in different types of acute lymphoblastic leukemia as well as closely related issues such as graft versus tumor effect, minimal residual disease, and conditioning therapies are discussed thoroughly. In addition, various modalities of novel therapies have been discussed to be efficacious in clinical practice.

Keywords: acute lymphoblastic leukemia, hematopoietic stem cell transplantation, reduced intensity conditioning, monoclonal antibodies, immunotherapies

1. Introduction

Acute lymphoblastic leukemia (ALL) is a clonal expansion or malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood, and extramedullary sites [1, 2]. It is a highly heterogeneous disease comprising several entities that have distinct clinical manifestations, therapeutic strategies as well as prognostic implications [2]. ALL can occur at any age, but 80% cases occur in children [1, 3]. The incidence of ALL follows a bimodal distribution with the first peak occurring in children 2–5 years of age, while the second peak

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is encountered around the age of 50 years [1, 3]. While most children with ALL are potentially curable, the prognosis in infants, adults, and elderly individuals remains poor [3].

Worldwide, different induction chemotherapeutic regimens are utilized in the treatment of patients with ALL [4–7]. Examples are—(1) USA and Canada: CCG series in children and CALGB in adults, modified DFCI 91-01 and 95-01, in addition to hyper-fractionated hyper-CVAD (cyclophosphamide, vincristine, cytarabine, dexamethasone, methotrexate, and doxorubicin); (2) UK: ALL-97, revised ALL-99 for children and UKALL XII for adults; (3) France: FRALLE-93 in children, LALA-94 in adults and GRAALL-2003; (4) Germany: pediatric DCOG-ALL or Berlin-Frankfurt-Munster [standard or augmented regimen]; (5) Italy: AIEPO [pediatric] and GIMEMA [adults]; (6) Holland and Belgium: HOVON-70; (7) Spain: PETHEMA ALL-96; (8) Sweden and Finland: pediatric NOPHO-92 and adult Nordic protocols; and (9) Mexico: LALIN (pediatric) and LALA (adult) [4–7]. Sometimes, different chemotherapeutic regimens are used in the same geographic location or even in the same country [4–7]. Additionally, these treatment regimens undergo modifications or even total replacement once new literature data or results of large studies become available [4–8]. Despite the development of several induction regimens, there is no single best regimen for induction therapy in ALL [4–8]. The main constituents of these chemotherapeutic regimens are almost similar with different dosing and treatment schedules and they include: daunorubicin, doxorubicin, or idarubicin; prednisolone or dexamethasone; vincristine; L-asparaginase; cyclophosphamide; 6-mercaptopurine; and intrathecal (IT) as well as intravenous (IV) methotrexate [4–8].

Recently, the more intensified pediatric ALL induction regimens have been used in adolescents and young adults (AYAs), 15–40 years of age, having ALL, and their use has been associated with superior response rates [4, 6, 9]. Several studies have shown that AYAs treated with adult chemotherapeutic regimens have poorer outcome compared with patients belonging to the same age group treated with pediatric-inspired regimens [4, 6, 9]. Additionally, certain cancer centers, such as Dana-Farber Cancer Center, USA, are currently treating patients between the ages of 1 and 50 years with the same regimens of chemotherapy [5]. The recent incorporation of novel and targeted therapies, such as tyrosine kinase inhibitors (TKIs), nelarabine and rituximab, into the induction therapy of ALL has further improved the response rates and the outcomes in general [4, 5, 10–12].

2. HSCT in ALL patients

2.1. GVL effect in ALL

Several studies have shown that (1) in adults with ALL receiving cytotoxic chemotherapy, the high incidence of relapse is the main cause of treatment failure, hence post-remission therapy particularly the efficacy of allogeneic hematopoietic stem cell transplantation (HSCT) is a critical issue; (2) the rates of relapse of ALL following HSCT are higher than those encountered in other hematologic malignancies; (3) relapse of ALL post-allogeneic HSCT is a major cause of treatment failure as it is associated with an extremely poor prognosis; (4) graft versus host disease (GVHD) encountered in the post-HSCT period has a protective effect against disease

relapse; and (5) graft versus leukemia (GVL) effect plays a major role in curing patients with ALL subjected to allogeneic HSCT [13–17]. However, there is considerable evidence for the existence of GVL effect after HSCT in patients with ALL: (1) relapse rates are lower in recipients of allogeneic HSCT compared with recipients of autologous grafts, (2) relapse rates are lower in patients who develop acute or chronic GVHD following allografts, and (3) the use of interferon immediately post-allogeneic HSCT may reduce relapse rate through stimulation of an immunological response [15, 18]. Unfortunately, the efficacy of GVL effect in the context of donor lymphocyte infusion (DLI) of ALL in the post-allogeneic HSCT setting is quite unimpressive as response rates to DLI in ALL patients receiving allografts have been reported to range from 0 to 18% [15, 18].

GVL effect in ALL is influenced by the extent of leukemia burden [15]. Minimal residual disease (MRD) studies after HSCT have found a strong correlation between the presence of MRD and relapse of leukemia [16]. Frequent MRD monitoring post-allogeneic HSCT may predict ALL relapse early enough, thus allowing the implementation of various approaches such as: (1) reduction of immunosuppressive therapy, (2) DLI, and (3) adoptive T-cell therapy, but such approaches may be ineffective in the presence of high disease burden [15, 16].

The development of GVHD following allogeneic HSCT in patients with B-cell ALL is associated with a lower probability of leukemia relapse due to a non-specific inhibition of B-lymphocytosis [19]. Also, the improved survival in recipients of allogeneic HSCT who develop acute or chronic GVHD is attributed to the beneficial GVL effect of GVHD [14]. Chronic GVHD, particularly limited form, is associated with a significant GVL effect [13]. However, the correlation between GVHD and GVL is mainly seen in non-T cell-depleted allografts [14]. The influence of chronic GVHD on the risk of relapse has been found to be prominent in patients with chromosomal translocations or normal cytogenetics [13].

Studies have shown that in ALL patients subjected to allogeneic HSCT, relapse rates are higher in: (1) patients receiving dual or effective GVHD prophylaxis as the intensity of the GVHD prophylactic regimen inversely correlates with the incidence of acute GVHD and (2) recipients of matched sibling donor (MSD) allografts compared with those receiving matched unrelated donor (MUD) grafts as MSD allogeneic HSCT is associated with reduced likelihood of GVHD and reduced treatment-related mortality (TRM), while MUD allografts are associated with higher incidence of GVHD and lower relapse rates due to the pronounced GVL effect of GVHD [14, 17, 20].

In ALL patients receiving allogeneic HSCT, GVL effects are associated with detectable Wilms tumor-1-specific T lymphocyte (WT1) [18]. These results support the immunogenicity of WT1 after HSCT for ALL and highlight the potential for WT1 vaccines to boost GVL effect after HSCT for ALL [18]. The lower relapse rates encountered in ALL patients receiving HSCT may indicate that viral antigens play a role in the induction of anti-leukemic effect [14].

2.2. MRD in ALL

Several studies have shown the prognostic relevance of detection of MRD in patients with ALL [21–23]. MRD identified prior to allogeneic HSCT is the strongest predictor of post-HSCT

relapse in ALL patients [23]. Thus, elimination of pre-HSCT MRD in patients with ALL by novel therapeutic approaches or drug combinations may decrease the risk of post-HSCT relapse and improve overall survival (OS) [23].

MRD evaluation or monitoring in ALL patients can be performed by: (1) flow cytometry, (2) real-time quantitative polymerase chain reaction (RT-Q-PCR), and (3) next-generation sequencing (NGS) [21, 22]. Currently, analysis of MRD is mostly performed by PCR analysis of immunoglobulin (IG) and T-cell receptor (TCR) gene rearrangements, and this method has sensitivity of 10^{-4} in patients with ALL [21, 24]. However, despite the broad clinical usefulness of MRD evaluation, false-positive MRD results can be obtained due to massive B-lymphocyte regeneration after HSCT [24].

NGS enables precise and sensitive detection of multiple antigen receptor rearrangements, thus providing more specific readout compared to RT-Q-PCR, and this will reflect positively on the treatment interventions in ALL patients undergoing HSCT [24]. MRD determines the outcome of autologous HSCT in patients with HR-ALL [25]. In patients with ALL planned for autologous HSCT, MRD evaluation by PCR or NGS may play a role in the direction of therapy as it can predict long-term relapse-free survival [26, 27]. For example, patients with SR-ALL who do not have HR features at diagnosis and who have pre-transplantation negative MRD can be offered autologous HSCT combined with maintenance therapy [26].

2.3. 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 that ranges between 25 and 40% [28, 29]. The post-remission therapies for patients with ALL generally include: (1) consolidation followed by maintenance chemotherapy, (2) allogeneic HSCT for high-risk (HR) patients, and (3) autologous HSCT for standard-risk (SR) patients or HR patients who do not have an HLA identical sibling donor [26, 29]. Therefore, after achieving first CR, intensive therapies, such as allogeneic HSCT and autologous HSCT, are generally offered to patients who are eligible for HSCT [28].

Autologous HSCT was first introduced as a treatment for ALL patients nearly 60 years ago [29]. However, autologous HSCT has been underutilized in ALL patients [29, 30]. Autologous HSCT performed in patients with ALL in CR1 has produced leukemia-free survival ranging between 45 and 65% [29]. Strategies to enhance autologous GVL effect after HSCT may enhance long-term survival in ALL patients subjected to autologous HSCT [31].

In patients with ALL, factors identifying patients who are at high risk of relapse include: (1) age more than 35 years, (2) T-cell type of ALL, (3) elevated white blood cell (WBC) count at presentation, (4) elevated serum lactic dehydrogenase (LDH) level at diagnosis, (5) extramedullary disease (EMD) prior to HSCT, (6) specific cytogenetic abnormalities, (7) blast cell proportion ≥5% on day 15 of induction therapy, and (8) having MRD at various stages during therapy [26, 27]. These factors indicate poor prognosis and decreased OS as well as disease-free survival (DFS) [26, 27]. Factors such as the risk features at the time of diagnosis and MRD following induction therapy greatly affect the outcome of autologous HSCT in ALL patients [29]. SR patients with

ALL who lack poor prognostic factors will benefit from autologous HSCT. Also, HR patients with ALL who are likely to benefit from autologous HSCT include: (1) rapid responders who achieve CR after the first induction therapy and (2) those with negative pre-HSCT MRD [25, 26, 28, 29]. In ALL patients, autologous HSCT should be performed after completion of consolidation chemotherapy as an alternative to maintenance chemotherapy [25]. Autologous HSCT combined with post-transplantation maintenance therapy could be a valid therapeutic option in adult patients with ALL [26, 30]. Adoptive immunotherapy and maintenance therapy after autologous HSCT reduce relapse rate and improve outcome in patients with ALL [30, 32]. Post-autologous HSCT maintenance therapy can be in the form of: (1) 6-mercaptopurine, methotrexate, vincristine, and prednisolone or (2) TKIs in patients with Philadelphia chromosome-positive (Ph+) ALL [27, 30]. Novel therapies, such as blinatumomab, may reduce the burden of MRD before stem cell collection prior to autologous HSCT, thus making the combination of novel therapies and autologous HSCT a real alternative to allogeneic HSCT and prolonged maintenance therapy for ALL patients [27]. Improved DFS and low relapse rates can be achieved after autologous HSCT in adults with ALL who (1) rapidly respond to the first induction chemotherapy and (2) achieve MRD prior to autologous HSCT [26, 28]. Long-term outcome of allogeneic HSCT is superior to autologous HSCT or maintenance chemotherapy [27–29]. Several studies have failed to demonstrate the superiority of autologous HSCT over chemotherapy in adult patients with ALL [27–29]. Before the era of novel therapies and haploidentical HSCT, the prognosis of patients with ALL who relapse post-autologous HSCT was reported to be dismal due to the few available therapeutic options [29].

2.4. Allogeneic HSCT conditioning therapies

Allogeneic HSCT cures hematologic malignancies through two major mechanisms: (1) pre-transplantation conditioning therapy that kills leukemic cells directly and (2) graft versus tumor (GVT) effect [33]. Over the past 25–30 years, the outcome of HSCT has been steadily improving due to improvements in: (1) conditioning therapies, (2) GVHD prophylaxis and therapy, (3) supportive care facilities, (4) new antifungal agents, (5) better diagnostic tools, (6) incorporation of novel and targeted therapies such as TKIs into conventional therapeutic regimens, and (7) donor selection by improvement of human leukocyte antigen (HLA) typing methods and the increased use of MUDs [13, 34, 35]. Also, the use of flow cytometry and PCR for evaluation of MRD and monitoring of early relapse has improved the outcome of HSCT further [34]. Pre-transplantation detection of MRD by flow cytometry or PCR has been associated with lower OS and relapse-free survival [34].

For the past 40 years, the standard myeloablative conditioning (MAC) regimen for ALL is composed of total body irradiation (TBI) 1200 cGy and IV cyclophosphamide 120 mg/Kg body weight [36, 37]. In patients with ALL, relapse is common after HSCT [37]. Attempts to decrease the risk of relapse following HSCT include: (1) modulation of the conditioning regimen by increasing TBI dose to >1200 cGy or adding a second chemotherapeutic agents such as etoposide and (2) decreasing the intensity of the conditioning regimen by relying on immune modulation, GVL effect, for disease control [36]. However, the optimal conditioning therapy for transplant-eligible patients with ALL has not been defined yet [38].

The MAC regimens for ALL consist of: TBI (1200–1400 cGy) in addition to one or more chemotherapeutic agents [36]. In children with ALL, the MAC therapies include: (1) TBI 1000–1200 cGy + cyclophosphamide, (2) TBI 1000–1200 cGy + cyclophosphamide + etoposide, (3) TBI 1320–1400 cGy + cyclophosphamide, and (4) TBI 1320–1400 cGy + cyclophosphamide + etoposide [36]. Studies have shown that (1) etoposide + fractionated TBI and cyclophosphamide + fractionated TBI are equally effective, (2) effectiveness of chemotherapy alone, such as IV busulfan + melphalan, conditioning therapy in patients with HR ALL, (3) there is an advantage of substituting etoposide for cyclophosphamide or increasing the TBI dose to ≥13 Gy when cyclophosphamide is used, and (4) treosulfan, etoposide, and cyclophosphamide conditioning regimen has favorable toxicity profile with lower NRM [33, 35, 39, 40].

In comparison to TBI-containing conditioning regimens, fludarabine and pharmacokinetic-targeted busulfan conditioning therapy appears to be safer and equally effective in controlling ALL [41]. Fludarabine + amsacrine + cytarabine (FLAMSA) + anti-thymocyte globulin (ATG) + fractionated TBI conditioning regimen followed by allogeneic HSCT is feasible and effective in patients with HR or relapsed ALL, thus presenting a potential alternative to the classical TBI and cyclophosphamide MAC therapy [37]. Studies have shown that (1) combination of busulfan and clofarabine provides an effective control while maintaining a favorable safety profile and has produced OS and NRM rates comparable to those achieved with traditional TBI-based conditioning regimens and (2) busulfan + fludarabine + ATG + TBI conditioning therapy has achieved excellent outcomes in all patients with ALL except older patients with comorbidities [38, 42, 43].

The incorporation of etoposide into the intensified conditioning regimens has been associated with improved disease control but at the expense of higher rates of toxicity and TRM [37]. Medium-dose etoposide, cyclophosphamide, and TBI conditioning therapy is suitable for adults with HR-ALL in CR1 and SR-ALL in CR2, below the age of 50 years, as it has been shown to be associated with: lower relapse rate, no increase in toxicity, and better OS [44, 45]. In children and adolescents with ALL, the addition of etoposide to TBI + cyclophosphamide conditioning regimen should be avoided due to increased risk of mortality. Also, TBI dose >1300 cGy should be avoided due to increased risk of second malignancy [36]. In children with ALL in CR1 and CR2, the incorporation of alemtuzumab, anti-CD52 monoclonal antibody, into the MAC therapy in MUD allografts has produced durable engraftment with low rates of GVHD and comparable rates of DFS to recipients of MSD transplants [46]. Thiotepa-based conditioning regimen for allogeneic HSCT in patients with ALL is feasible and effective, and it has produced main outcomes comparable to those achieved by other conditioning therapies [47]. In children with ALL transplanted in second CR, the 3-year DFS using MAC followed by allogeneic HSCT has been reported to range between 30% and 70% [48].

Reduced intensity conditioning (RIC) regimens have been used extensively in adults with hematologic malignancies including ALL [48]. In MAC regimens, relapse protection is provided by dose-intensive chemotherapy ± TBI, while in RIC regimens, relapse protection is provided by GVL effect [44, 48]. The indications for RIC-allogeneic HSCT include: (1) old age, (2) poor performance status, (3) active infection, (4) significant organ dysfunction, and

(5) presence of comorbid medical conditions [44, 48]. Compared with MAC regimens, RIC regimens have been associated with acceptable rates of donor engraftment and lower rates of TRM [48]. In children with ALL, the use of RIC regimens has achieved long-term DFS, but it has been associated with high rates of TRM, acute and chronic GVHD, myelosuppression, and disease relapse [44, 48]. In adult patients with HR-ALL receiving umbilical cord blood transplantation (UCBT): (1) MAC regimens have been associated with DFS comparable to that reported with other stem cell sources and (2) the results of RIC regimens are encouraging [49]. New therapeutic strategies for adults with ALL are increasingly utilized with better outcomes and they include: (1) various TKIs for Ph+ ALL, (2) pediatric inspired chemotherapeutic regimens for Philadelphia chromosome-negative (Ph−) ALL, and (3) HLA-haploidentical HSCT [44]. However, the optimal therapeutic modality should be selected after taking the following factors into consideration: age of the patient, Philadelphia chromosome positivity, donor availability, disease risk stratification, and efficacy as well as safety of the therapeutic measure [44].

2.5. Allogeneic HSCT in ALL

Cytogenetic abnormalities occur in 60–85% of patients with ALL. However, numerical chromosomal abnormalities, alone or in association with structural changes, occur in 50% of ALL patients [2, 50, 51]. The most common chromosomal abnormalities that are encountered in patients with ALL are listed in **Table 1** [2, 50, 51]. In patients with ALL, certain HR features predict poor long-term outcome even in patients receiving intensive chemotherapy. These HR features are shown in **Table 2** [2, 3, 50, 52–55]. Patients having HR features, including HR cytogenetic abnormalities and genetic mutations, are less likely to respond well to chemotherapy and are more likely to relapse. Hence, this category of patients may require not only more intensified chemotherapeutic regimens but also novel therapies as well as HSCT in order to have optimal control of their leukemia [2, 3, 50, 52–55]. The main indications of allogeneic HSCT in children and adults with ALL are shown in **Table 3** [7, 23, 51–54, 56–65].

In adults with ALL, post-remission therapies include: consolidation chemotherapy followed by maintenance therapy, autologous HSCT, and allogeneic HSCT [66, 67]. There is controversy regarding the role of frontline allogeneic HSCT for patients with ALL in CR1 [68]. However, three meta-analyses showed potential benefit of allogeneic HSCT in CR1 [67–69]. These three meta-analyses included 41 studies and they came to the following conclusions: (1) myeloablative MSD allografts had absolute survival benefit of 10–15% at 5 years compared to chemotherapy alone or chemotherapy followed by autologous HSCT, (2) MSD allografts improve survival in patients younger than 35 years and are the optimal post-remission therapy in ALL patients ≥15 years old, (3) no beneficial effect of autologous HSCT in comparison to chemotherapy, and (4) MSD allografts offer superior OS as well as DFS and significantly reduce the risk of relapse but carry increased risk of NRM [67–69]. For patients with relapsed and refractory ALL, allogeneic HSCT is the only potentially curative therapeutic modality [68]. Three major studies that included 1419 patients with relapsed ALL in adults showed that the prognosis of relapsed ALL in adults was very poor and that the 5-year OS of adults with relapsed ALL not subjected to allogeneic HSCT ranged between 0.0 and 10% [70–72].

1. Philadelphia chromosome [t9,22]: The commonest cytogenetic abnormality. Encountered in 15–30% of adults and 5% of children with ALL
2. Chromosomal abnormalities that are associated with higher risk of central nervous system involvement:
• t4,11
• t8,14
• t14q+
3. Chromosomal abnormalities that are associated with:
• High white cell and blast cell counts at presentation
• High risk of relapse
• t9,22
• t4,11
4. Other common cytogenetic encountered in patients with ALL:
• t10,14
• t1,14
• Deletion 11q22
• Deletion 11q23 [MLL]
• Hypodiploidy
• Hyperdiploidy

ALL, acute lymphoblastic leukemia and MLL, mixed lineage leukemia.

Table 1. The most common chromosomal abnormalities in patients with ALL.

Either MAC therapies or RIC regimens can be offered according to the age and comorbid medical conditions of the HSCT recipient [73, 74]. In patients with acute leukemia, the following stem cell sources have been utilized in allogeneic HSCT: MSD, MUD, and UCB [73, 75].

2.6. Focus on haploidentical HSCT

Haploidentical HSCT evolved several decades ago, and it has undergone several modifications and remarkable developments in relation to: conditioning therapy, post-transplantation immunosuppression, and graft manipulation [73, 76]. Historically, the main obstacles to successful haploidentical HSCT were graft failure, intractable GVHD, decreased GVL effect, and delayed immune reconstitution [75, 76]. This form of HSCT is readily available for the majority of patients with acute leukemia and is an acceptable alternative to other donor sources of stem cells [75–77]. Techniques that are used to improve the outcome of haploidentical HSCT include: (1) CD3/CD19 depletion to reduce GVHD, (2) KIR B haplotype donors

http://dx.doi.org/10.5772/intechopen.73562

1. **Age:** <1 year and >35 years
2. **White blood cell count at presentation:**
   - > 30,000 in B-lineage
   - > 100,000 in T-lineage
3. **Cell type:** pro-B; early and mature T
4. **Immunophenotyping:**
   - CD 20 positivity
   - CD 10 negative pre-B ALL.
5. **Poor performance status:** >1
6. **Poor response to prednisolone**
7. **Peripheral blood blasts ≥5% on day: 8–15**
8. **Failure to achieve remission >4 weeks of induction chemotherapy**
9. **Involvement of central nervous system**
10. **Clinical relapse:** >First complete remission
11. **Minimal residual disease:** Detectable molecular and immunophenotypic evidence of disease while in morphologic remission.
12. **High-risk cytogenetic and molecular abnormalities:**
    - +8
    - –7
    - Deletion 6q
    - Low hypodiploidy
    - Near triploidy
    - Immunoglobulin H gene rearrangement
    - Intrachromosomal amplification of chromosome 21
    - Translocation 8,14
    - Translocation 4,11
    - Translocation 1,19
    - Translocation 9,22
    - Philadelphia-like
    - Complex cytogenetics

13. High-risk genetic mutations:
• IKZF1 deletion [IKAROS]
• Unmutated NOTCH1
• MLL [mixed lineage leukemia] gene rearrangement: 11q23
• RAS-PTEN altered
• JAK 2 mutation
• KMT2A rearrangement
• CREBBP
• CRLF2
• ETP
• PBX-E2A+
• BAALC+

Table 2. High-risk features that predict poor long-term outcome even with intensive chemotherapy in patients with acute lymphoblastic leukemia.

confer rapid natural killer cell proliferation soon after HSCT resulting in lower relapse rates due to GVL effect, and (3) infusion of high numbers of CD34+ cells to improve immune reconstitution [77].

Historically, mega doses of stem cells had been used after T-cell depletion in order to avoid development of GVHD, but this maneuver had been associated with high incidence of graft failure and disease relapse [73, 78]. Recently, unmanipulated allografts and post-transplantation cyclophosphamide have been used with high success [73, 74, 78]. Also, it has been shown that the outcome of unmanipulated haploidentical HSCT in adult patients with acute leukemia are comparable to those of unrelated UCBT and MUD allografts [74, 78].

Adults	Children
1. Philadelphia chromosome-positive ALL in CR1	**1.** Severe hypodiploidy
2. ALL with Philadelphia-like molecular signature	**2.** Persistent MRD
3. High-risk or very high-risk ALL in CR1	**3.** T-cell ALL with poor response to prednisolone
4. Relapsed ALL [ALL in CR2 or beyond]	**4.** Primary induction failure
5. Primary refractory disease [ALL refractory to induction or first-line chemotherapy]; once CR is achieved following salvage therapy, allogeneic HSCT can be performed	**5.** MLL gene rearrangement in infants with ALL
6. Presence of MRD at any stage during the course of the disease, regardless their initial risk group [standard risk or high risk]	**6.** Relapsed ALL [ALL in CR2]: bone marrow or extramedullary relapse
7. MLL [mixed lineage leukemia] gene rearrangement	

ALL, acute lymphoblastic leukemia; CR, complete remission; MLL, mixed lineage leukemia; and MRD, minimal residual disease.

Table 3. Indications of allogeneic HSCT in patients with ALL.

In patients with Ph− ALL in CR1, studies have shown that (1) outcomes of haploidentical HSCT are comparable to MSD and MUD allografts and (2) outcomes of HR patients are comparable to those of low-risk patients once haploidentical allografts are used. Therefore, haploidentical HSCT represents a valuable alternative for patients with Ph− ALL lacking MSDs [79, 80]. In adult patients with HR-ALL in CR1, haploidentical HSCT performed with post-transplantation cyclophosphamide-based GVHD prophylaxis has produced 52% DFS at 3 years, thus providing a suitable alternative to HLA-matched transplantation [68].

Also in adults with HR-ALL in CR1 and CR2 or beyond, unmanipulated haploidentical transplants have been associated with 3-year OS and DFS of 33 and 31%, respectively; thus, unmanipulated haploidentical allografts can be considered a valid option for adults with HR-ALL lacking HLA-identical donors particularly if performed in early disease status [74]. Compared to HLA-matched related donor allografts, haploidentical HSCT has produced similar rates of long-term survival and NRM but lower relapse rates in patients with Ph+ ALL, thus haploidentical HSCT represents a valid therapeutic option for patients who lack a suitable HLA-matched donor [81, 82].

2.7. HSCT in T-cell ALL

T-cell ALL is an aggressive neoplasm derived from malignant transformation of lymphoblasts committed to T-cell lineage [83]. It accounts for 10–25% of all cases of ALL [84–86]. Given the rarity of T-cell ALL, patients are typically treated in a similar fashion to B-cell ALL with pediatric inspired dose-intense multi-agent chemotherapy regimens in addition to central nervous system (CNS) prophylaxis [83–85]. T-cell ALL carries a poor prognosis compared with B-cell ALL due to: (1) higher relapse rates even if they respond to chemotherapy and achieve CR and (2) more extensive involvement of bone marrow and extramedullary sites, particularly the mediastinum [83, 84, 86]. Even with the current intensive chemotherapeutic regimens, the 5-year event-free survival (EFS) is 80%, whereas the 10-year EFS is only 15% [84].

Allogeneic HSCT is a potentially curative therapeutic option for patients with T-cell ALL, but relapse after allogeneic HSCT is a major cause of treatment failure [86]. Patients with T-cell ALL who lack an HLA-matching donor for allogeneic HSCT should preferably have prolonged maintenance chemotherapy [83]. Studies have shown that (1) in children with T-cell ALL in CR2 subjected to allogeneic HSCT, the 3-year OS is about 50% and (2) in adults with T-cell ALL including the aggressive early-thymic precursor (ETP) subtype subjected to allogeneic HSCT in CR1, the 3-year OS is 62% and those transplanted in CR2 or beyond, the 3-year OS is 24% indicating the better outcome of allogeneic HSCT in CR1 in adults [84, 85]. Other studies on adults with T-cell ALL subjected to allogeneic HSCT have shown the following results: (1) allogeneic HSCT is safe and effective in overcoming the poor prognosis particularly when applied early, (2) there was controversy regarding the use of TBI in the conditioning therapies as some studies highlighted the importance of having TBI as part of the conditioning regimen, while other studies showed no difference between TBI-based and busulfan-based conditioning therapies, and (3) MRD status at transplantation is highly predictive of disease relapse, suggesting that novel therapies

can be offered before and after allogeneic HSCT to improve the outcome of this group of patients [85–88]. Patients with refractory T-cell ALL can be treated successfully with unmanipulated allografts from HLA-mismatched haploidentical siblings as haploidentical HSCT offers higher GVL effect [89, 90].

Nelarabine, a prodrug of Ara-G, has shown selective cytotoxicity against T-cell lymphoblasts and is usually used in relapsed and refractory T-cell ALL [83, 91]. Nelarabine is a valuable therapeutic option in patients with T-cell ALL relapsing after allogeneic HSCT as it has shown response rates reaching 81%; hence it should be considered in: (1) treating relapses post-allogeneic HSCT and (2) maintenance therapy following transplantation in HR patients [91].

Gamma delta subtype of precursor T-cell ALL is usually treated with the same intensive chemotherapeutic regimens like other types of ALL (T- and B-cell types) [92]. In this rare type of T-cell ALL, the preferred therapy is usually induction chemotherapy to achieve CR followed by upfront allogeneic HSCT to eradicate the potential residual disease by the GVT effect of allogeneic HSCT [92].

2.8. HSCT in Ph+ ALL

Philadelphia chromosome positivity is the most common recurrent cytogenetic abnormality observed in adult patients with ALL [93–95]. Approximately 20–25% of adults and only about 2% of children with ALL harbor Philadelphia chromosome and express the bcr-abl transcript [93, 96, 97]. In recent years, the most significant therapeutic advancement has been the introduction of TKIs into the therapeutic regimens of Ph+ ALL [94]. In the era before TKIs, patients with Ph+ ALL were having poor prognosis after standard chemotherapy with DFS rates ranging between 0.0% and 20% [94, 96]. Historically, adult Ph+ ALL had been associated with high relapse rates and short DFS and OS [98].

Results of autologous HSCT in adults with Ph+ ALL are still disappointing [99]. Studies have shown that (1) Ph+ ALL is incurable without allogeneic HSCT and (2) in patients with Ph+ ALL, particularly adults, who are eligible for HSCT and who have achieved CR allogeneic HSCT, has remained the consolidation therapy of choice and the only proven curative therapeutic strategy [94, 96, 98–101]. However, patients with Ph+ ALL planned for allogeneic HSCT can be divided into three risk groups or categories: (1) HR; positive MRD or overt clinical disease, (2) intermediate risk; molecular disease but without morphologic disease, and (3) low risk; no evidence of MRD [96].

In children and adolescents with Ph+ ALL, allogeneic HSCT is a controversial issue and there is increasing reluctance to offer allogeneic HSCT to children in the era of TKIs [94, 97, 102]. The children's Oncology Group reported the following results on the use of TKIs in children and adolescents with Ph+ ALL: (1) excellent outcomes of the combination of TKI and chemotherapy with OS of 88% at 3 years and 70% at 5 years, (2) achievement of complete hematological remission in approximately 95% of cases and molecular remission in >50% of patients, and (3) no advantage of subjecting patients to allogeneic HSCT [103, 104]. On the contrary, in children and young adults with Ph+ ALL, studies have shown that (1) results

of allogeneic HSCT are superior to chemotherapy alone, (2) MSD and MUD allografts have yielded equivalent outcomes, (3) in patients subjected to allogeneic HSCT, age, WBC count at presentation, and early response to treatment have been shown to be independent prognostic indicators, (4) early allogeneic HSCT is recommended once morphologic remission is achieved as this form of treatment has shown to produce durable remissions in patients with CR1, and (5) in children with Ph+ ALL, two studies showed advantage of allogeneic HSCT in protection against late disease relapses and in achieving 5-year OS and DFS of 80.2 and 72.9%, respectively [105–108].

In patients with Ph+ ALL, achievement of complete molecular remission (CMR) prior to allogeneic HSCT reduces the risk of leukemia relapse post-allogeneic HSCT even though TKIs may still rescue some patients who relapse after transplantation [109, 110]. Without TKIs, 30–50% of patients with Ph+ ALL relapse after allogeneic HSCT [96]. Even in the era of TKIs, relapse is still the main cause of allogeneic HSCT failure in HR patients Ph+ ALL [111]. Ph+ ALL patients, subjected to allogeneic HSCT, should ideally be (1) in CR and without MRD prior to transplantation and (2) below 60 years of age. However, only carefully selected patients ≥60 years old are candidates for allogeneic HSCT [100, 112]. In patients with Ph+ ALL, RIC allogeneic HSCT can be offered to older patients and those with comorbidities, that is, patients who are ineligible for MAC therapy [100, 112].

Additional cytogenetic abnormalities, such as monosomy 7, and abnormalities of chromosomes 8 and 9 are common in patients with Ph+ ALL as they are encountered in two thirds of cases [113]. Pre-existing mutations in the ABL kinase domain are frequently associated with resistance to TKIs and are a common cause of post-HSCT relapse in patients with Ph+ ALL [101]. Pre-transplantation risk factors for relapse in patients with Ph+ ALL include: (1) expression of P190 transcript, (2) evidence of morphologic disease at the time of transplantation, and (3) type of donor, with recipients of autologous HSCT or MSD having the highest risk of relapse [96]. Post-transplantation risk factors for relapse in patients with Ph+ ALL include: (1) expression of P190 transcript which carries the highest risk of relapse, (2) detection of MRD by reverse transcription PCR for bcr-abl transcript, and (3) lack of chronic extensive GVHD [96]. These risk factors can be utilized to improve risk stratification for patients with Ph+ ALL undergoing HSCT in order to develop specific strategies or therapeutic plans [96]. In patients with Ph+ ALL subjected to allogeneic HSCT, TKI therapy tailored according to pre-transplantation TKI response, anticipated toxicities, and Abl-1 domain mutations is feasible and may reduce relapse rate and improve the outcome of patients [111].

2.9. Relapse of ALL before and after HSCT

Approximately 20–25% of ALL patients experience relapses of their disease at 5 years from diagnosis and initial therapy despite receiving the standard chemotherapeutic regimens [114, 115]. The prognosis of children and young adults with relapsed ALL is poor [114, 115]. Only a minority of adults with ALL who relapse after first line therapy can be rescued [116]. Salvage chemotherapy in patients with relapsed ALL includes: (1) mitoxantrone, etoposide, and cytarabine or (2) fludarabine, cytarabine, pegylated-asparaginase, and granulocyte colony stimulating factor [116]. Salvage chemotherapy alone is not curative in relapsed ALL [115].

Allogeneic HSCT offers the best and may be the only chance for cure in relapsed ALL, particularly in adult patients [114–116]. Allogeneic HSCT can be performed using either a sibling donor or an unrelated donor [114, 115].

In patients with ALL, relapse after HSCT remains the main cause of treatment failure due to the limited therapeutic options and the associated poor outcome [117–119]. Factors that affect the occurrence as well as the outcome of ALL relapse after HSCT include: GVHD, MRD, intrinsic factors of the disease, and transplantation characteristics [120]. The prognosis of patients with ALL who relapse after HSCT is extremely poor with long-term survival <10%, and there is no difference in short-term survival between patients with isolated EMR and systemic relapse, suggesting that all disease relapses should be treated systemically [118]. EMR after allogeneic HSCT poses significant challenge for transplantation physicians as it carries poor outcome and has limited therapeutic options [119]. The risk factors for EMR, particularly CNS relapse, after allogeneic HSCT include: HR cytogenetics, advanced disease status, male gender, history of EMD before HSCT, hyperleukocytosis at diagnosis, and receiving peripheral blood stem cells [119]. However, prophylactic IT chemotherapy and maintenance treatment after HSCT may reduce the rate of CNS relapse post-HSCT [119].

Treatment of ALL relapse post-HSCT includes: (1) continuation of low-dose immunosuppressive therapy may be the optimal approach as abrupt discontinuation of immune suppression does not lead to any clinical benefit and may result in aggravation of GVHD, (2) re-induction or salvage therapy followed by second allogeneic HSCT in highly selected patients may offer the best chance of prolonged survival, and (3) other interventions, such as frequent MRD monitoring, pre-emptive immunotherapy in the form of DLI, post-transplantation maintenance therapy, use of novel and targeted therapies in post-HSCT, and enrollment in clinical trials [117, 118, 120].

Prerequisites for successful management of ALL post-HSCT relapse by either second allogeneic HSCT or experimental non-transplant approaches include: good clinical condition of the patient and the capacity to achieve hematological remission by the salvage therapy [117]. For patients with acute leukemia who relapse after the first allogeneic HSCT, only a second allograft can provide a realistic chance of long-term disease remission [121]. The second allogeneic HSCT used in the treatment of relapse after the first allograft can be obtained from HLA-MSD, MUD, or HLA-mismatched alternative donor [122]. Based on the rapid donor availability as compared to MUD, a haploidentical second allogeneic HSCT might be considered as an alternative therapeutic option for relapse after the first allograft [122, 123].

3. Novel and targeted therapies in ALL

3.1. Tyrosine kinase inhibitors

The introduction of TKIs has revolutionized the therapy of patients with Ph+ ALL [94, 107]. Over the past 12 years, administration of TKIs before allogeneic HSCT has significantly improved the long-term outcome of allogeneic HSCT in adults with Ph+ ALL [93, 107]. In

http://dx.doi.org/10.5772/intechopen.73562

patients with Ph+ ALL, TKIs have been incorporated into: (1) the induction phase in conjunction with cytotoxic chemotherapy, (2) in the consolidation and maintenance phases in conjunction with cytotoxic chemotherapy in patients who are not eligible for allogeneic HSCT, and (3) in the post-transplantation maintenance therapy in recipients of allogeneic HSCT and their incorporation into the treatment regimens at various stages of the disease has significantly improved the outcomes of patients [10–12, 93, 124].

3.1.1. Imatinib

Studies in children with Ph+ ALL have shown that (1) the incorporation of imatinib into the chemotherapeutic regimens has improved the prognosis and (2) TKIs administered in the early phases of therapy can dramatically reduce MRD and improve the outcome of patients [12, 94, 124, 125]. Also, several groups have reported that the combination of imatinib and high dose chemotherapy has significantly improved the outcome of children and adults with Ph+ ALL with CR rates reaching 86–95% and 1-year OS reaching 75% [94, 124]. The 4-year OS in Ph+ ALL subjected to allogeneic HSCT in the era of imatinib has increased significantly to reach 52% [94]. Imatinib maintenance following allogeneic HSCT may further improve the outcome of patients with Ph+ ALL [125].

3.1.2. Dasatinib

Dasatinib is a second-generation TKI with dual Src and Abl kinase inhibition activity [126, 127]. It is active against all imatinib-resistant kinase domain mutations apart from T315I mutation, thus having superior potency for inhibiting bcr-abl fusion protein compared to imatinib [126, 127]. The use of dasatinib is associated with the following adverse effects: bone marrow suppression, fluid retention, pleural effusion, skin eruptions, cardiac conduction disturbances, and colitis that may be hemorrhagic, immune-mediated, or cytomegalovirus-induced [127].

Dasatinib is usually used in combination with cytotoxic chemotherapy such as hyper-CVAD regimen to control Ph+ ALL prior to allogeneic HSCT [126]. It can also be used in the setting of post-HSCT as maintenance therapy to prevent disease relapse or to eliminate MRD [127]. In older adults who are not candidates for allogeneic HSCT or younger patients who are unable to tolerate intensive chemotherapy, an induction regimen composed of targeted therapies such as dasatinib and corticosteroids may offer the potential of greater and longer responses, thus avoiding the morbidity associated with the use of cytotoxic chemotherapy [128, 129]. In this combination, dasatinib inhibits Scr-Abl kinase while corticosteroids modulate Bcl2 family of proteins leading to apoptosis [128]. The combination of dasatinib and corticosteroids is associated with relapses mainly due to T315I mutations that can be further treated with ponatinib [129].

3.1.3. Nilotinib

The use of TKIs, including the second-generation drugs such as nilotinib, in the post-HSCT setting in patients with Ph+ ALL could potentially reduce relapse rates [130, 131]. Studies

on the use of nilotinib have shown the following results: (1) safety and efficacy of nilotinib prophylaxis to prevent relapse of Ph+ ALL after allogeneic HSCT, (2) effectiveness of nilotinib to control MRD and to convert patients to CMR, and (3) achievement of prolongation of survival without jeopardizing immune function or reconstitution following HSCT [130–133]. However, side effects such as prolongation of QT interval on electrocardiogram and early disease relapse post-HSCT may limit its use [132, 134].

3.1.4. Ponatinib

Ponatinib is a pan-bcr/abl TKI which is capable of inhibiting T315I kinase domain mutation that confers resistance to other TKIs and dismal prognosis [95, 129]. Ponatinib can be given prior to HSCT as bridging therapy to control disease and to prevent disease relapse following HSCT [95, 135]. Rapid hematological responses can be obtained in almost all patients but morphologic and molecular responses can unfortunately be short-lived [95]. One study showed that patients with Ph+ ALL who underwent allogeneic HSCT had better survival than those who received ponatinib alone [136].

3.2. Nelarabine

Nelarabine is a purine nucleoside analogue and a soluble prodrug of Ara-G with specific cytotoxicity against T-lymphocytes [136–145]. It has significant activity in patients with T-cell ALL and T-cell lymphoblastic lymphoma (LBL) [137, 140, 142, 143, 146]. In October 2005, nelarabine gained an accelerated approval by the food and drug authority (FDA) in the USA for the treatment of children and adults with T-cell ALL and T-cell LBL who are in relapse or refractory to at least two chemotherapeutic regimens [137–145]. It has been used as a single agent or in combination with intensive chemotherapy or P13K inhibitors [138, 142, 143, 146–148]. The use of nelarabine in the treatment of patients having T-cell ALL relapsing after allogeneic HSCT has been associated with 90% OS at 1 year [144]. The adverse effects of nelarabine include: (1) myelosuppression with neutropenia and thrombocytopenia and (2) neurotoxicity, which is the commonest side effect, may be transient and reversible and can manifest as depression in the level of consciousness, sensory and motor neuropathies, and Guillain-Barre syndrome [139–145]. The mechanisms of resistance to nelarabine include: (1) reduced drug incorporation into DNA and (2) anti-apoptosis [149]. Other novel purine analogues, such as clofarabine and forodesine, have demonstrated significant anti-tumor activity in relapsed/refractory T-cell ALL and T-cell LBL [138].

3.3. Blinatumomab

Blinatumomab is a bispecific T-cell engager monoclonal antibody construct that is designed to direct cytotoxic T-cells to CD19-expressing B-cells [150, 151]. It is indicated (1) in the treatment of Ph− relapsed/refractory pre-B ALL, (2) to induce GVL reaction in patients with pre-B ALL relapsing post-allogeneic HSCT, and (3) in the treatment of HR patients with Ph+ ALL [150, 151]. In a phase II single arm multicenter study that included 45 patients with HR-Ph+ ALL patients who had relapsed or were refractory to TKIs, single agent blinatumomab showed remarkable anti-leukemic activity as 88% of patients achieved CR or CR with partial hematologic recovery and a median OS of 7.1 months [151]. The adverse effects

of blinatumomab include: fever, febrile neutropenia, headache, neurotoxicity, such as aphasia, and cytokine release syndrome (CRS) [140].

3.4. CAR T-cells

Chimeric antigen receptors (CAR) consist of an extracellular antigen recognition domain linked to an intracellular signaling domain [152, 153]. An important part of CAR design in choosing an optimal tumor-associated antigen to target [152]. A patient's own T-cells may be genetically modified to express an artificial T-cell receptor termed CAR designed to be specific to a tumor-associated antigen [154]. CARs are artificial receptors that redirect antigen specificity, activate T-cells, and further enhance T-cell function through their costimulatory component [155]. Ideally, the target antigen should only be expressed on tumor cells and not on normal cells in order to ensure that there is no (on-target-off tumor) activity that could result in toxicity [152]. The most extensively investigated CAR in clinical setting targets CD19, which is expressed not only in most B-cell malignancies but also in normal B-cells. Thus, CAR-mediated tumor destruction is accompanied by CAR-mediated destruction of normal B-cells resulting in B-cell aplasia [152].

Center	Patients (number and diagnosis)	Viral transduction	Conditioning therapy	Cytokine release syndrome (%)	Outcome
Memorial Sloan Kettering Cancer Center	**27** Relapsed B-ALL	Retroviral transduction	Cyclophosphamide	**18**	• 88% CR • Molecular CR: 70%
University of Pennsylvania and Children Hospital of Philadelphia	**25** Pediatric R/R B-ALL	Lentiviral transduction	No conditioning therapy	**27**	• 90% morphologic remission • 73% MRD by flow cytometry • 6 patients relapsed
Fred Hutchinson Cancer Research Center	**9** Phase I	Lentiviral transduction	Cyclophosphamide	**33.3**	• 7 patients had CR with 5 having MRD
MD Anderson Cancer Center	**10** CAR T-cells infused following allogeneic HSCT	Sleeping beauty transposon electroporation	No conditioning therapy	**30**	• 10 patients achieved CR at 5 months

ALL, acute lymphoblastic leukemia; R/R, relapsed/refractory; CR, complete remission; HSCT, hematopoietic stem cell transplantation; CAR, chimeric receptor antigen; and MRD, minimal residual disease.

Table 4. Clinical trials on the use of CAR-T cells in ALL patients.

1. Monoclonal antibodies, immunotoxins, and immunoconjugate antibodies:

- CD20:
  - Rituximab
  - Obinutuzumab
  - Ofatumumab
  - REGN 1979
- CD 22:
  - Epratuzumab
  - Inotuzumab ozogamicin (IO)
  - Moxetumomab pasudotox, reformulation of BL22
- CD 19:

a. Single CD 19 monoclonal antibodies:

- Coltuximab ravtansine [SAR3419]
- Denintuzumab mafodotin [SGN-CD19A]
- ADC-402, newest CD19 monoclonal antibody

b. Dual monoclonal antibodies including anti-CD19 activity:

- Combotox: Anti-CD19 and anti- CD22
- Bispecific T cell engager (BITE) construct: Blinatumomab [anti-CD3; CD 19 construct]

2. Proteasome inhibitors: Bortezomib

3. JAK inhibitors: Ruxolitinib

4. Hypomethylating agents: Decitabine

5. P13K- mTOR inhibitors:

- NVP-BEZ 235
- NCT01756118
- NCT 02484430
- NCT 01523977
- NCT 01403415
- NCT 01614197
- NCT 01184885

6. Chimeric antigen receptor T-cells (CAR T-cells)

Table 5. Novel and targeted therapies in acute lymphoblastic leukemia.

CAR T-cell therapy involves several laboratory, technical, and clinical procedures that include: (1) obtaining peripheral blood mononuclear cells by leukapheresis, (2) CD3 (T-cell) separation, (3) engineering of T-cells to express CAR by gene transfer technology, viral transduction, or

genetic modification with CD19-specific CAR to target tumor in addition to cell expansion, (4) lymphodepletion by administration of pre-infusion conditioning therapy in the form cyclophosphamide or cyclophosphamide and fludarabine, (5) CAR T-cell infusion to target CD 19+ B-cells, and (6) cell death or apoptosis of CD19+ lymphoblasts [152–154, 156]. Indication for CAR T-cell therapy include: (1) relapsed and refractory B-cell ALL, (2) chronic lymphocytic leukemia, (3) acute myeloid leukemia, (4) follicular lymphoma, (5) diffuse large B-cell lymphoma, (6) multiple myeloma, (7) Waldenstrom's macroglobulinemia, and (8) treatment of relapse post-allogeneic HSCT for B-cell malignancies [152, 157, 158]. Studies have shown that treatment options in relapse after allogeneic HSCT for lymphoid malignancies including ALL include: (1) DLI, (2) salvage chemotherapy followed by a second allogeneic HSCT, and (3) CAR T-cell infusions, a cell-based immunotherapy that can effectively enhance and maintain antitumor GVL response after transfusion into patients [152, 157, 158].

Adverse effects or complications of CAR T-cell therapy in relapsed and refractory ALL include: (1) CRS, which can be severe and life-threatening, may manifest with: hyperpyrexia, hypotension, capillary leak syndrome, neurological manifestations, myalgia, and respiratory as well as renal insufficiency, (2) neurotoxicity in the form of delirium and seizures, (3) macrophage activation syndrome, (4) aplasia of normal B-lymphocytes, and (5) death that may occasionally be encountered [155, 159–165]. Serum biochemical markers of CRS following CAR T-cell therapy in relapsed and refractory ALL include C-reactive protein and ferritin [155, 159, 165]. Management of CRS includes: supportive care, corticosteroids, vasopressors, ventilatory support, and anti-interleukin-6 receptor antibody (tocilizumab) therapy [165]. The main clinical trials on the use of CAR T-cells are shown in **Table 4** [152, 156]. Novel and targeted therapies that can be used in the treatment of patients with ALL are shown in **Table 5** [1–3, 56, 160, 161].

4. Future directions

Recently, management of patients with ALL has improved dramatically due to several reasons such as improvements in our understanding of the disease biology; improvements in the diagnostic techniques, including molecular genetics, that help in disease stratification; improvements in supportive care; adoption of dose-intense pediatric-inspired chemotherapeutic regimens in AYAs; progress in HSCT including donor selection, conditioning therapies, and prevention as well as treatment of GVHD; monitoring of MRD; and the availability of several novel agents and targeted therapies in addition to cellular and immunotherapies. The availability of the modern therapeutic interventions has translated into improved response rates and outcomes including OS. The integration of various novel and targeted therapies before and after transplantation has further improved the outcomes of patients with ALL.

Different therapeutic interventions available for treating children and adults with ALL should be considered complementary to each other. Future studies should focus on the optimal integration of these novel therapies into the treatment paradigm of this malignancy in order to achieve higher rates of response, disease control as well as long-term survival. Risk stratification of ALL will help in tailoring the management of patients according to their risk category taking into consideration their clinical manifestations, laboratory findings, including cytogenetic and molecular profiles, as well as responses to therapeutic interventions.

In children with ALL, the role of HSCT has decreased due to the use of intensified chemotherapeutic regimens and the incorporation of novel and targeted therapies into the upfront treatment. However, patients with HR features, those with MRD, and patients with relapsed or refractory disease should be considered for HSCT and novel therapies should be administered whenever indicated.

5. Conclusion

Intensified pediatric chemotherapeutic regimens show poor outcome of ALL in adults compared to children particularly in patients with HR features or disease relapse. Thus, allogeneic HSCT has more indications in adults than in children. However, the integration of other therapeutic interventions into the management of ALL, before and after transplantation, is likely to improve the outcome of patients further.

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