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REVIEW ARTICLE

Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT)

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Abstract

Allogeneic hematopoietic stem cell transplantation (HSCT) in first complete remission is a standard of care for adult patients with Philadelphia chromosome (Ph)-negative acute lymphoblastic leukemia (ALL) and high risk of relapse. However, the stratification systems vary among study groups. Inadequate response at the level of minimal residual disease is the most commonly accepted factor indicating the need for alloHSCT. In this consensus paper on behalf of the European Working Group for Adult Acute Lymphoblastic Leukemia and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation, we summarize available evidence and reflect current clinical practice in major European study groups regarding both indications for HSCT and particular aspects of the procedure including the choice of donor, source of stem cells and conditioning. Finally, we propose recommendations for daily clinical practice as well as for planning of prospective trials.

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Introduction

Allogeneic (allo) hematopoietic stem cell transplantation (HSCT) is considered an effective treatment for preventing relapse in patients with Philadelphia chromosome (Ph)-negative acute lymphoblastic leukemia (ALL), combining myeloablative doses of chemotherapy and/or radiotherapy with potential beneficial graft-versus-leukemia reaction mediated by T cells of donor origin. Unfortunately, it is also associated with significant incidence of non-relapse mortality (NRM), reaching 15% after alloHSCT from matched sibling donors (MSD) and 22% for HSCT from unrelated donors (URD) [1]. Therefore, the use of alloHSCT is weighed against the reduction of the risk of relapse and the risk of NRM. However, despite attempts to elaborate prognostic scores, the estimation of these measures is uneasy and therefore potential benefit from alloHSCT in many individual cases is uncertain [2, 3].

Furthermore, all prospective studies evaluating the role of alloHSCT for adults with ALL have been conducted considering the availability of human leukocyte antigen (HLA) identical MSD, while the majority of alloHSCTs nowadays are preformed using URD [4]. Moreover, in recent years, the number of HSCTs from mismatched related donors (MMRD), mostly haploidentical donors have been growing [5]. In addition, the use of transplantations with reduced intensity conditioning (RIC) allowed for wider application of alloHSCT to patients at older age and those with comorbidities. In contrast, the use of autologous (auto)HSCT decreased over time due to negative results of some prospective trials; however, with strict monitoring of MRD it is conceivable that some patient populations may benefit from this treatment option [6].

Altogether, the role of both alloHSCT and autoHSCT for adults with Ph-negative ALL requires re-evaluation. In view of lack of prospective, randomized studies addressing this issue in the modern era, detailed indications for HSCT are based mainly on expert opinions and vary among countries. The goal of the current review was to summarize available evidence and reflect current clinical practice in major European study groups. Furthermore, we were able to establish a position statement elaborated by leading investigators representing the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and experts from the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT).

Prospective studies on the role of HSCT in adults with ALL

Before the era of routine MRD assessment

In the 1980s and 1990s, several prospective studies have been conducted based on genetic randomization. Patients in first complete remission (CR1) having MSD were offered alloHSCT, while those lacking MSD were treated with either autoHSCT or conventional-dose maintenance chemotherapy.

In three studies (Bordeaux-Grenoble-Marseille-Toulouse study, GOELAL02 trial, HOVON-18/37 trial) alloHSCT was compared with autoHSCT [7–9]. All of them demonstrated superiority of allogeneic transplantation in terms of leukemia-free survival (LFS).

In a LALA-87 study, patients who achieved CR and had MSD were assigned to allograft, whereas those without a donor were randomized to receive either autoHSCT or conventional-dose chemotherapy [10]. Intention-to-treat analysis showed increased overall survival (OS) for patients having a donor (46% vs. 31% at 10 years, $p = 0.04$). The advantage was significant for high-risk ($p = 0.009$) but not for standard-risk ALL ($p = 0.06$). In a following LALA-94 trial, a similar design was applied for patients with high-risk ALL [11]. In both Ph-negative and Ph-positive groups, having a donor was associated with significantly increased probability of 3-year LFS. No advantage of autoHSCT over chemotherapy could be demonstrated.

Another two studies comparing MSD-HSCT, autoHSCT and conventional-dose chemotherapy as a post-consolidation treatment of adults with high-risk ALL were performed by the PETHEMA and EORTC groups, respectively [12, 13]. In these studies, however, no significant differences between study arms could be demonstrated.

The Medical Research Council (MRC) UKALL XII/ECOG 2993 was the largest study based on "genetic" randomization, including 1646 adults with both standard- and high-risk ALL [14]. Patients received two phases of induction and, if in remission, were assigned to alloHSCT if they had MSD. Remaining patients were randomized to chemotherapy for 2.5 years or autoHSCT. A donor versus no-donor analysis restricted to patients with Ph-negative ALL showed superiority of alloHSCT (OS, 53% versus 45% at 5 years, $p = 0.01$). The survival difference was significant in standard-risk but not in high-risk patients due to a high NRM (36% at 2 years) in the latter group. Patients randomized to chemotherapy had a higher 5-year OS rate than those assigned to autoHSCT (46% vs. 37%, $p = 0.03$).

Taken together, results of the above cited studies provided rationale to use alloHSCT as a tool to prevent relapse in adults with ALL in CR1. However, identification of patients who most likely benefit from alloHSCT or in whom this treatment option could be avoided remained uncertain. Furthermore, it has been demonstrated that autoHSCT is inferior to conventional-dose consolidation, and its use after consolidation does not provide substantial benefit.

In the era of routine MRD assessment

Several methods have been elaborated to assess MRD in adults with ALL [15]. For patients with Ph-positive ALL, detection of BCR-ABL transcript by real-time quantitative polymerase chain reaction (PCR) is preferred. In Ph-negative ALL, MRD may be assessed either by detection of leukemia-specific phenotype using multiparameter flow cytometry or clonally rearranged genes encoding for immunoglobulin/T-cell receptor chains by PCR. Sensitivity of PCR-based methods is higher compared to flow cytometry; however, both were found feasible in clinical routine with high concordance of the results [16]. MRD positivity was demonstrated to be the most important prognostic factor for relapse in ALL. Its effect is independent from the presence of conventional risk factors. In the PALG 4-2002 study, a multivariate analysis revealed that only MRD level $>10^{-3}$ after induction (hazard ratio (HR) = 3.07, $p = 0.0002$), age >35 years (HR = 2.36, $p = 0.009$) and initial leukocyte count $>30 \times 10^9$/L (HR = 1.85, $p = 0.04$) significantly influenced the risk of relapse [17]. In a pooled analysis from the GMALL 06/99 and 07/03 trials, the persistence of MRD after induction and/or consolidation was associated with significantly shorter duration of CR. The difference was particularly distinct among patients who were not treated with alloHSCT [18]. In another GMALL study focused on patients with standard-risk ALL, who completed 1 year of chemotherapy, detection of MRD following previous MRD-negative status was associated with 61% relapse rate compared to only 6% in patients with continuous MRD negativity [19]. Therefore, both inadequate early response and late MRD appearance should be considered for risk stratification.

Bassan et al. [20] published the first prospective study, in which MRD status was taken into account for decisions regarding alloHSCT. MRD was tested at weeks 10, 16 and 22 using real-time quantitative PCR with one or more sensitive probes. Only patients with t(9;22) or MLL rearrangement were immediately eligible for alloHSCT. Among remaining patients those with negative or low positive ($<10^{-4}$) PCR signal at week 16 and totally undetectable signal at week 22 were treated with maintenance chemotherapy. Patients not fulfilling the above criterion were candidates for alloHSCT. MRD positivity was detected in 54 out of 112 evaluable patients among whom 36 (67%) individuals were actually treated with alloHSCT. MRD level was found to be the most important prognostic factor for LFS (72% vs. 14% at 5 years, $p = 0.001$). Among MRD-negative patients, the LFS rates were independent of the presence of conventional risk factors. Therefore, the authors concluded that MRD analysis during early post-remission therapy improves risk categorizations and reinforces risk-oriented strategies.

In the PETHEMA ALL-AR03 trial, patients with high-risk Ph-negative ALL showing good early morphological response (<10% blasts in bone marrow at day 14 of induction) and MRD level assessed by flow cytometry less than 5×10^{-4} at the end of consolidation were assigned to delayed consolidation and maintenance chemotherapy [21]. AlloHSCT was scheduled only in patients with poor early morphological response or MRD level $\geq 5 \times 10^{-4}$, and was actually performed in 50 out of 71 assigned individuals. The probability of LFS at 5 years for respective cohorts was 55 and 32% ($p = 0.002$), respectively. However, in the analysis restricted to patients with "stringent" high-risk features, i.e., high initial leukocyte count, unfavorable immunophenotype or adverse karyotype, the difference was no longer statistically significant (52% vs. 38%, $p = 0.11$), suggesting that the use of alloHSCT may partially overcome negative prognostic impact of MRD positivity.

In two subsequent trials (GRALL-2003 and GRALL-2005) by the French/Belgium/Swiss group, 522 Ph-negative ALL patients up to the age of 55 years, with high-risk features, as assessed based on conventional criteria, were intended for alloHSCT from either MSD or URD [22]. Among these, 282 (54%) actually received a transplant in CR1. Induction and consolidation regimens were intensified following the pediatric protocols. MRD was monitored by PCR after the first course of induction and after three blocks of consolidation. In a time-dependent analysis, the authors examined post hoc the impact of alloHSCT on the overall outcome. AlloHSCT was associated with longer LFS in patients with post-induction MRD $\geq 10^{-3}$ (HR = 0.40, $p = 0.001$) but not in good MRD responders.

Subsequently, results of MRD assessment have been incorporated in stratification systems of Ph-negative ALL by many study groups. It may be used to identify patients who require alloHSCT despite lack of other high-risk features as well as those patients in whom alloHSCT may be avoided despite belonging to the high-risk group. However, the strategies may depend on the specific chemotherapy protocols and sensitivity of MRD techniques. It should be emphasized that chemotherapy backbone in most of above cited studies was very intensive, and pediatric inspired. These protocols may produce high cure rate even without alloHSCT [23]. In many countries, however, this is not routine and less intensive regimens, e.g., hyperCVAD (fractionated cyclophosphamide, vincristin, doxorubicin, dexamethasone), are commonly used across the world. In such a case the relevance of MRD negativity may not necessarily be as strong as in pediatric-like protocols and the indications for alloHSCT should be probably based on conventional risk factors in addition to MRD status. Similar dilemma is regarding patients who cannot tolerate intensive chemotherapy and require dose reductions and treatment delays. Finally, following results of the MRC UKALL XII/ECOG 2993 study, even standard-risk patients having MSD may be considered candidates for alloHSCT [14].

According to a retrospective, single-center analysis from Duarte (CA, USA), cytogenetics does not impact on outcome of adults with ALL [24]. In recent years, however, some new molecular subtypes have been identified, including Ph-like ALL, characterized by gene expression profile similar to Ph-positive ALL in the absence of *BCR/ABL1* rearrangement. It is associated with poor prognosis in both children and adults [25, 26]. According to small data reported by Jain et al. [26], achieving MRD negativity does not change inferior long-term outcomes in this setting. There is lack of data of whether alloHSCT is superior to pediatric-inspired regimens for Ph-like ALL. Prospective studies are needed to define if all these patients should be treated with alloHSCT regardless of the MRD status.

Similar dilemmas regard early thymic precursor (ETP) ALL which is a high-risk subgroup of T-lineage ALL characterized by specific stem cell and myeloid features [27]. According to the analysis by the French group, including 47 adults with ETP-ALL, the rate of MRD positivity after induction was significantly higher compared to other patients with T-cell ALL [28]. However, the use of alloHSCT was associated with marked improvement of results leading to comparable outcomes. The authors suggested that the use of response-based risk stratification and therapy intensification abrogates the poor prognosis of adult ETP-ALL and that there is no need to elaborate strategies specific for this subtype. On the other hand, in another study by the French group focused on T-cell ALL, some molecular features were shown to have strong impact on outcome independently of the MRD status [29]. High-risk molecular subgroup was defined as: no *NOTCH1/FBXW7* mutation and/or *N/K-RAS* mutation and/or *PTEN* gene alteration. These patients as well as those with complex karyotype (≥5 abnormalities) are postulated to be candidates for alloHSCT [29, 30].

Transplant options for adults with ALL

Types of donor

Several donor types may be considered for adults with ALL. Initially MSDs predominated, but with increasing number of unrelated volunteers, URD-HSCT became the most popular option. According to a recent EBMT report focused on adults with ALL, between years 2010 and 2012, transplantations from unrelated donors accounted for 52% of all procedures, followed by MSD-HSCT (37%), MMRD-HSCT (5%) and autoHSCT (6%) [31].

Several reports suggested that results of MSD-HSCT and URD-HSCT for patients with ALL may be comparable. In an analysis by Tomblyn et al. [32], the use of well-matched or partially matched URD was not associated with inferior outcome compared to MSD. In a Japanese study the OS rates after URD-HCT and MSD-HCT for ALL patients in CR1 were superimposable; however, HLA disparities were associated with increased risk of NRM [33]. According to a recent analysis by the EBMT, results of alloHSCT for adults with ALL in CR1 improved significantly over time with 2-year LFS rates reaching 60% for both MSD- and URD-HSCTs performed between years 2008 and 2012 [1]. However, in a multivariate model, the use of URD was associated with significantly increased risk on NRM (HR = 2.11, $p = 0.002$) and overall mortality (HR = 1.52, $p = 0.01$). In that study, 29% of URD-HSCTs were performed across single (22%) or double (7%) HLA antigen or allele mismatches.

MSD and matched URD are considered preferable options for ALL patients in need of alloHSCT. However, a significant proportion of ALL patients still lack HLA-compatible donor and therefore require alternative approaches. In such a case either mismatched URD, MMRD or unrelated cord blood may be considered. In recent years, family haploidentical donors, who may include either children, parents or the majority of siblings, have become more and more practiced following the introduction of new immunosuppressive protocols based on post-transplant use of cyclophosphamide, allowing for unmanipulated graft without ex vivo T-cell depletion [5, 34]. According to a recent analysis by the EBMT, including 91 patients with ALL in CR1, the probability of LFS at 3 years after unmanipulated MMRD-HSCT was 47% [35]. Similar results (52% LFS rate) were reported by Srour et al. [36].

Unrelated cord blood transplantation (UCBT) is another alternative option for ALL patients lacking MSD. The report by Marks et al. [37] comparing UCBT and URD-HSCT showed equivalent adjusted survival. Similarly, in a recent study by the Japanese group, no significant differences could be demonstrated for adult patients with ALL treated with either UCBT, 8/8 matched URD bone marrow transplantation or 7/8 matched unrelated donor transplantation [38]. However, in contrast to MMRD-HSCT, the application of UCBT in Europe tends to decrease, probably due to the high cost of the procedure [5].

Considering all alternative donor options, it may be stated that in the modern era all ALL patients being in need of alloHSCT may be offered such treatment. On the other hand, further comparative, large-scale analyses are needed to estimate risks and benefits associated with particular procedures.

In contrast to alloHSCT, the role of autoHSCT for patients with Ph-negative ALL appears questionable and the number of procedures is decreasing [31]. The outcome of autoHSCT is mainly affected by the MRD status at the time of transplantation [6].

Conditioning

Total body irradiation (TBI) is considered a standard backbone for myeloablative conditioning in adults with ALL. Although it

has never been prospectively evaluated, results of numerous retrospective analyses indicated its advantage over chemotherapy-based regimens mainly thanks to reduced risk of relapse (HR = 0.48, $p = 0.004$, according to recent analysis by the EBMT) [1, 39–41]. It must be stressed, however, that TBI methods are very heterogeneous in terms of the dosage, timing and many technical aspects, and therefore insufficiently standardized at the international level [42]. As well, the optimal chemotherapy counterpart of TBI has not been defined, so far.

The most practiced regimen includes 12 Gy TBI applied in 6 fractions in combination with cyclophosphamide (Cy) at the total dose of 120 mg/kg. However, some retrospective analyses suggested that the combination with etoposide may be more effective, especially for patients transplanted in CR2 [43, 44]. Furthermore, according to the study by Marks et al. [43], patients treated with alloHSCT in CR2 benefited from TBI dose ≥13 Gy as compared to <13 Gy, in terms of reduced risk of relapse and improved LFS. The Japanese group performed a retrospective study comparing 1178 ALL patients treated in first or subsequent CR with Cy/TBI and 376 ALL patients receiving Cy/TBI in combination with intermediate doses of etoposide (VP16, 30–40 mg/kg) [45]. The latter was associated with decreased risk of relapse (HR = 0.75, $p = 0.05$) and improved LFS (HR = 0.76, $p = 0.01$). According to the study by the EBMT the number of TBI fractions may be safely reduced to 3 or 4, which makes the application of TBI easier from the logistical point of view [46].

The use of TBI may be associated with increased risk of late adverse effects, including secondary solid tumors [47]. Hence, attempts to substitute it by introducing novel chemotherapy-based protocols have been done. According to a retrospective analysis by Mitsuhashi et al. [48], the use of intravenous (i.v.) instead of oral busulfan in combination with cyclophosphamide may be associated with results comparable to TBI [48]. However, the number of patients treated with i.v. busulfan was relatively small ($n = 40$). Kebriaei et al. [49] compared results of 819 patients who received TBI combined with etoposide or cyclophosphamide and 299 patients treated with i.v. busulfan combined with either cyclophosphamide, melphalan, fludarabine or clofarabine [49]. In a multivariate model the use of busulfan was associated with a significantly higher risk of relapse (HR = 1.46, $p = 0.002$) but similar NRM, LFS and OS. The authors concluded that i.v. busulfan-based conditioning is a valuable option for patients who cannot tolerate TBI [49]. Alternative approaches include the use of regimens based on high doses of thiotepa. Thiotepa penetrates the blood–brain barrier which may be important for preventing relapses in central nervous system. Initial reports, including retrospective analysis by the EBMT, show encouraging results [50]. Further studies are needed to confirm non-inferiority of thiotepa- compared to TBI-based regimens.

The introduction of RIC or non-myeloablative regimens allowed for wider application of alloHSCT to older patients with ALL as well as to those with significant comorbidities. Although the role of RIC-alloHSCT for older adults with ALL has never been prospectively evaluated, data from retrospective reports are encouraging. According to recent analysis by the Center for International Blood and Marrow Transplant Research (CIBMTR), evaluating 273 ALL patients aged 55 years or older with B-cell ALL, including 50% with Ph-positive disease, the probability of OS at 3 years was 45%, provided that the transplantation was performed in CR1 [51]. In contrast to myeloablative preparative regimens, the RIC ones are more frequently based on chemotherapy than irradiation [31]. The spectrum of RICs is very wide and data comparing particular regimens for adults with ALL are pending. In a prospective UK NCRI UKALL14 study, 186 patients aged 40 years or older were treated with RIC-alloHSCT in first CR [52]. The conditioning consisted of fludarabine, melphalan and alemtuzumab. The probabilities of OS and event-free survival at 2 years were 63 and 56%, respectively. Post-induction MRD level was the only factor independently influencing the risk of relapse (HR = 4.14).

Source of stem cells

In 2010, the vast majority of alloHSCT procedures are being performed using peripheral blood as a source of stem cells, although prospective trials demonstrated increased risk of chronic graft-versus-host disease (GVHD) after peripheral blood compared to bone marrow transplantation from either MSD or URD [53]. In prospective studies comparing both sources of stem cells, patients with ALL constituted minority, therefore any specific conclusions regarding the effect on the overall outcome could be drawn. Results of a retrospective analysis by the EBMT suggest a trend towards reduced risk of relapse for peripheral blood transplants (HR = 0.69, $p = 0.06$), without significant effect on NRM, LFS or OS [1].

It has been demonstrated that the risk of chronic GVHD may be decreased by the use of anti-thymocyte globulin (ATG) as a part of conditioning regimen [54–56]. Once again, prospective, randomized studies addressing this issue were not specifically focused on adults with ALL. More recently, a retrospective analysis has been performed on behalf of the EBMT, including patients with Ph-negative ALL treated with either MSD-HSCT or URD-HSCT in CR1 [57]. The use of ATG was associated with reduced incidence of chronic GVHD without significant impact on LFS or OS. Therefore, it seems that ATG-based conditioning may be effectively and safely applied to patients with ALL. Further analyses are needed to define optimal dose, brand and timing as well as to evaluate if the effect is independent of the type of donor.

HSCT for Ph-negative ALL in CR1: current clinical practice

Indications for "younger" adults

In order to reflect current clinical practice regarding utilization of HSCT for patients with Ph-negative ALL, representatives of 11 European study groups were asked to provide their local guidelines. Data from 11 study groups have been collected.

As listed in Table 1, the indications for alloHSCT in CR1 are highly heterogeneous. Similarly, the cut-off age limit for patients to be considered candidates for intensive induction–consolidation followed by myeloablative HSCT varies with a range of 40 years to 65 years. Among younger patients, positive MRD status is the only risk factor accepted across all study groups; however, relevant cut-off levels as well as time-points selected for treatment decisions are not consistent. Four study groups consider MRD level to be of clinical relevance both after induction and consolidation, in four study groups only assessment during/after consolidation is taken into account, while in one study group only MRD after two blocks of induction is used for decision regarding the indications for alloHSCT. For most of the study groups, post-induction MRD level of $>10^{-3}$ of bone marrow nucleated cells is considered as high-risk feature, while the corresponding cut-off level after consolidation is usually 10^{-4} of bone marrow nucleated cells. Both molecular methods and flow cytometry are used for MRD assessment in current clinical practice, although the use of PCR-based methods predominates. Among other potential prognostic factors, high initial leukocyte count, especially for patients with B-lineage ALL, as well as adverse cytogenetic/molecular features are considered for treatment decisions regarding the use of alloHSCT by the majority of study groups. Two study groups include adverse immunophenotype, while single study groups include initial involvement of central nervous system, age >30 years or poor reduction of bone marrow blast during induction for risk stratification. For three ALL study groups, MRD level is considered the only surrogate driving clinical decisions regarding the use of alloHSCT. AlloHSCT is most frequently scheduled after the first course of consolidation.

Finally, only 4 out of the 11 ALL study groups accept autoHSCT as a treatment option for younger patients with Ph-negative ALL in first CR. This option is restricted to patients with low or negative MRD status.

Indications for "older" adults

According to a retrospective analysis by the EBMT, alloHSCT for ALL patients older than 60 years is associated with 35% LFS rate at 3 years [58]. In four ALL study groups, alloHSCT is an option for all "older" patients with Ph-negative ALL being in CR1 (Table 2). In another four ALL study groups, the indications are restricted to patients with poor risk features, in particular poor response at MRD level. Two study groups do not consider alloHSCT for older patients with Ph-negative ALL at all, while in one group the decision depends on a local policy of particular centers.

Three ALL study groups accept autoHSCT as a treatment option for "older" individuals with Ph-negative ALL and low or negative MRD status despite lack of evidence to support this strategy.

Choice of donor

In all study groups, MSD is the preferable donor choice for patients being candidates for alloHSCT. In all but one study group, 10/10 matched URD is also acceptable (Table 3). The choice of alternative donors varies among countries. URD with single HLA mismatch and haploidentical donors are considered as preferred or optional by almost all ALL study groups. However, URD with two HLA mismatches and UCB are considered as options by four and six study groups, respectively.

Summary of the position statement

1. AlloHSCT is an effective treatment option to prevent relapse in adults with Ph-negative ALL.
2. The use of alloHSCT in CR1 is recommended in all patients with features indicating high risk of relapse, among which the persistence of MRD is the strongest predictor. Monitoring of MRD using either molecular methods or flow cytometry should therefore be mandatory. AlloHSCT is recommended in all patients with persistent MRD. The acceptable level of MRD after induction is $<10^{-3}$ of bone marrow cells, while after consolidation it should be undetectable. Selection of other factors used for stratification (e.g., high initial leukocyte count, adverse genetics or adverse immunophenotype) should depend on specific chemotherapy protocol and experience of particular centers or study groups.
3. For patients treated with intensified (pediatric-inspired) chemotherapy protocols who achieve MRD-negative status, the use of alloHSCT in CR1 may not be required despite the presence of other high-risk factors.
4. HLA-identical sibling or matched unrelated donors are the preferred donors for alloHSCT. Patients with high risk of relapse lacking HLA-matched donor may

Table 1 Indications for HSCT in younger adults with Ph-negative ALL

Study group	Age (years)[a]	AlloHSCT	AutoHSCT	Method for MRD assessment	Preferred timing of alloHSCT
CELL (Czechia)	<65	At least one: •MRD $\geq 10^{-3}$ after induction •MRD $\geq 10^{-4}$ after consolidation	Option, if MRD negativity before 1st consolidation	PCR	After 1st cycle of consolidation
FALL (Finland)	<45	At least one: •WBC $>100 \times 10^9$/L •11q23 aberrrations •Hypodiploidy •B-lineage: – No CR after first course of induction – MRD $\geq 10^{-3}$ on day 79 •T-lineage: – Bone marrow blast count ≥25% on day 15 and ≥5% after block A of consolidation – MRD $\geq 10^{-3}$ after block B of consolidation	No	PCR and/or FC	After 1st cycle of consolidation
GIMEMA (Italy)	<65	At least one: •MRD positivity after consolidation •WBC $>100 \times 10^9$/L •Early/mature T-ALL, pro-B-ALL •t(4;11) •*MLL* rearrangement	Option, if MRD negativity after consolidation	PCR	After 1st cycle of consolidation
GMALL (Germany)	<55	At least one: •Common/pre-B-ALL and WBC $>30 \times 10^9$/L •Pro-B-ALL/*MLL* rearrangement •Early/mature T-ALL •No CR after induction I •MRD $\geq 10^{-4}$ after consolidation I	No	PCR	After 1st cycle of consolidation
GRAALL (France)	<60	At least one: •MRD $\geq 10^{-3}$ after induction •MRD $\geq 10^{-4}$ after consolidation	No	PCR	After consolidation
HOVON (The Netherlands)	<40	At least one: •MRD $\geq 10^{-4}$ during/after consolidation •No CR after first course of induction •Adverse cytogenetics •WBC $>30 \times 10^9$/L in B-ALL or WBC $>100 \times 10^9$/L in T-ALL	No	FC	After intensification 1
PALG (Poland)	<55	At least one: •MRD $\geq 10^{-3}$ after induction •MRD $\geq 10^{-4}$ during/after consolidation •WBC $>30 \times 10^9$/L in B-ALL or WBC $>100 \times 10^9$/L in T-ALL •*MLL* rearrangement •CNS involvement	Option, if all: •MRD $<10^{-3}$ after induction •MRD $<10^{-4}$ after consolidation	FC after induction PCR after consolidation	After consolidation
PETHEMA (Spain)	<55 (60 if "fit")	At least one: •MRD $>10^{-3}$ after induction •MRD $>10^{-4}$ during/after consolidation	No	FC	After 1st cycle of consolidation (if MRD$>10^{-3}$ after induction) After consolidation (if

Table 1 (continued)

Study group	Age (years)[a]	AlloHSCT	AutoHSCT	Method for MRD assessment	Preferred timing of alloHSCT
					MRD $>10^{-4}$ after consolidation)
RALL (Russia)	<55	B-cell ALL, at least one: •Age >30 years •WBC $>30 \times 10^9$/L •t(4;11), t(1;19) •MRD positivity during/after consolidation T-cell ALL: •*MLL* rearrangement	•T-cell ALL, except for *MLL* rearrangement	FC or PCR	After consolidation
SVALL (Sweden)	<65	At least one: •Leukemic blast count ≥5% after induction •MRD $\geq 10^{-3}$ after consolidation •Optionally for MLL rearrangement and hypodiploidy with low MRD level	No	B-cell ALL: FC T-cell ALL: PCR	After consolidation
UKALL (UK)	<40	At least one: •High initial WBC •Adverse cytogenetics •MRD $\geq 10^{-3}$ after two cycles of induction	No	PCR	After 2 cycles of induction

MRD minimal residual disease, *PCR* polimerase chain reaction, *FC* flow cytometry, *ALL* acute lymphoblastic leukemia, *CR* complete remission, *CNS* central nervous system, *WBC* white blood cell

[a]Cut-off age defining eligibility for intensive induction–consolidation chemotherapy and hematopoietic stem cell transplantation with myeloablative conditioning regimen

be offered transplantation from mismatched related (including haploidentical) donor or unrelated donor with single HLA allele/antigen disparity. Transplantation of cord blood is an alternative.

5. TBI-based myeloablative conditioning is the preferable one in young patients. TBI may be combined with either Cy or etoposide. In centers with limited access to TBI, chemotherapy-based conditioning using either i.v. busulfan or thiotepa may be considered. For elderly patients or patients with comorbidities, reduced intensity conditioning based on either TBI or chemotherapy is recommended.
6. Either peripheral blood or bone marrow may be used as sources of stem cells. In case of peripheral blood transplants, the use of in vivo T-cell depletion should be considered in order to reduce the risk of chronic graft-versus-host disease.

Future perspectives

Results of prospective, randomized studies to prove the MRD-based strategy are pending. A German study group is currently running a randomized trial comparing alloHSCT with consolidation chemotherapy for patients achieving MRD negativity after induction. Results of this study will verify prognostic relevance of conventional risk factors. For patients with MRD persistence, the introduction of monoclonal antibodies like bispecific T-cell engager blinatumomab has been demonstrated to provide a very high rate of molecular remissions [59, 60]. So far, however, it remains unclear whether this intervention may allow avoidance of alloHSCT. Novel agents like inotuzumab ozogamycin (conjugate of anti-CD22 monoclonal antibody with calicheamicin) used as front-line therapy in combination with reduced-dose chemotherapy are also postulated to increase the treatment efficacy [61]. With blinatumomab used as consolidation, followed by maintenance, the need for alloHSCT may be limited [62]. This hypothesis requires verification in prospective trial. On the other hand, blinatumomab is also being tested as maintenance after alloHSCT in order to reduce the risk of relapse. Future studies will probably evaluate the role of chimeric antigen receptor T cells or natural killer cells as well as check-point inhibitors for ALL patients in remission. The combination of above-mentioned options may replace alloHSCT in future or be complementary to transplant procedure. So far,

Table 2 Indications for HSCT in older adults with Ph-negative ALL

Study group	Age (years)[a]	AlloHSCT	AutoHSCT
CELL (Czechia)	>65	Option, if MRD $\geq 10^{-4}$ after 1st consolidation; according to center policy	Option, if MRD negativity after 1st consolidation
FALL (Finland)	>45	At least one: •Adverse genetics i.e.: t(4;11), MLL-AF4, t(17;19), TCF3-HLF •Early/mature T-ALL •No CR after first course of induction •MRD $>10^{-4}$ after 2 consolidation blocks •Increasing MRD (>1 log in two consecutive measurements separated by 2 weeks)	No
GMALL (Germany)	>55	Option for all patients	No
GIMEMA (Italy)	>65	Option, if MRD $\geq 10^{-4}$ after 1st consolidation	Yes, if MRD negativity
GRAALL (France)	>60	Option, according to center policy	No
HOVON (The Netherlands)	>40	1. Option for all patients having MSD or 10/10 matched URD. 2. Option for alternative donor HSCT (haploidentical/cord blood/ mismatched URD), if at least one: •Adverse cytogenetics •No CR after first induction course •WBC $>30 \times 10^9$/L in B-ALL or WBC $>100 \times 10^9$/L in T-ALL	No
PALG (Poland)	>55	Option, if at least one: •MRD $\geq 10^{-3}$ after induction •MRD $\geq 10^{-4}$ during/after consolidation	Option, if all: •MRD $<10^{-3}$ after induction •MRD $<10^{-4}$ during/after consolidation
PETHEMA (Spain)	>55 (60 if "fit")	Option for all patients	No
RALL (Russia)	>55	No	No
SVALL (Sweden)	>65	No	No
UK NCRI (UK)	>40	Option for all patients having MSD or 8/8 matched URD	No

MRD minimal residual disease, *ALL* acute lymphoblastic leukemia, *CR* complete remission, *MSD* matched sibling donor, *URD* unrelated donor, *WBC* white blood cell

[a]Cut-off age defining ineligibility for intensive induction–consolidation chemotherapy and hematopoietic stem cell transplantation (HSCT) with myeloablative conditioning regimen

Table 3 Choice of donor for patients with indications for alloHSCT

Study group	Matched sibling	Matched unrelated	Mismatched unrelated (9/10)	Mismatched unrelated (8/10)	Haploidentical	Unrelated cord blood
CELL (Czechia)	Yes	Yes	Yes	No	Option	No
FALL (Finland)	Yes	Yes	Option	Option	Option	Option
GMALL (Germany)	Yes	Yes	Yes	No	No	No
GIMEMA (Italy)	Yes	Yes	Yes	No; option	Option	Option
GRAALL (France)	Yes	Yes	Yes	No	No	No
HOVON (The Netherlands)	Yes	Yes	Option	No	Option	Yes
PALG (Poland)	Yes	Yes	Option	No	Yes	No
PETHEMA (Spain)	Yes	Yes	Option	No	Option	Yes
RALL (Russia)	Yes	No	No	No	Option <30 y.o.	No
SVALL (Sweden)	Yes	Yes	Option	Option	Option	Option
UKALL (UK)	Yes	Yes	Option	Option	Option	Yes

however, these perspectives regard patients with B-lineage ALL while not T-cell ALL.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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