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**REVIEW**

# Autologous stem cell transplantation for adult acute leukemia in 2015: time to rethink? Present status and future prospects

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The use of autologous stem cell transplantation (ASCT) as consolidation therapy for adult patients with acute leukemia has declined over time. However, multiple randomized studies in the past have reported lower relapse rates after autologous transplantation compared with chemotherapy and lower non-relapse mortality rates compared with allogeneic transplantation. In addition, quality of life of long-term survivors is better after autologous transplantation than after allogeneic transplantation. Further, recent developments may improve outcomes of autograft recipients. These include the use of IV busulfan and the busulfan+melphalan combination, better detection of minimal residual disease (MRD) with molecular biology techniques, the introduction of targeted therapies and post-transplant maintenance therapy. Therefore, ASCT may nowadays be reconsidered for consolidation in the following patients if and when they reach a MRD-negative status: good- and at least intermediate-1 risk acute myelocytic leukemia in first CR, acute promyelocytic leukemia in second CR, Ph-positive acute lymphocytic leukemia. Conversely, patients with MRD-positive status or high-risk leukemia should not be considered for consolidation with ASCT.

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## INTRODUCTION

During the past three decades, autologous stem cell transplantation (ASCT) has been widely used as consolidation therapy in patients with AML in first (CR1) or second (CR2), and to some extent in patients with ALL. Although ASCT remains a therapeutic option for AML, it has become less popular because of the high incidence of relapse (RI)[1] and the development of allogeneic hematopoietic stem cell transplantation (allo-HSCT), which has become feasible for almost all patients. Although the RI after allo-HSCT is lower because of the graft-versus-leukemia effect, this treatment is associated with higher rates of non-relapse mortality (NRM), GvHD and infection. Therefore, transplant survivors tend to have a poorer quality of life compared with patients who undergo ASCT.[2–4]

New treatment approaches have increased interest in ASCT for consolidation therapy in AML. Similarly, the use of tyrosine kinase inhibitors (TKI) for Ph-positive ($Ph^+$)/BCR-ABL-positive ALL and introduction of post-transplant maintenance therapy warrant a reassessment of ASCT in ALL.

## HISTORICAL BACKGROUND

ASCT was developed in the late 1970s as an alternative treatment for the 75% of patients who lacked an HLA-identical sibling. Bone marrow was initially the preferred source of stem cells and was sometimes manipulated before cryopreservation to purge residual leukemic cells *in vitro*.[5–8] However, since 1994 mobilized PBSC grafts have been shown to be feasible after conventional consolidation courses[9] with high-dose cytarabine, with faster kinetics of engraftment for neutrophils and platelets. PBSC have replaced bone marrow in $>80\%$ of cases.[10,11] For patients with AML, ASCT has been widely used for consolidation therapy in CR1 or CR2,[5] whereas use of this modality has been more limited in ALL.[12–15] The European Society for Blood and Marrow Transplantation (EBMT) registry presently contains data on 25 000 patients who have undergone ASCT for acute leukemia, and an estimated 50 000 patients throughout the world have been treated with ASCT.

### ASCT in AML

From 1990 to 2000, numerous randomized studies of patients with AML have compared ASCT with chemotherapy or allo-HSCT using HLA-identical sibling donors.[16–19] A meta-analysis published in 2004 included a total of 1044 patients with AML in CR1[20] who were randomly assigned to treatment with ASCT versus non-myeloablative chemotherapy. Patients who underwent ASCT had a lower RI and better leukemia-free survival (LFS) compared with the other treatment group. However, overall survival (OS) was similar between groups; high NRM and the use of salvage ASCT in CR2 are possible explanations for these findings. A second meta-analysis published in 2010,[21] which included 13 studies, led to similar conclusions. Of interest was the US intergroup study,[17] which compared ASCT with genoidentical allo-HSCT or several courses of high-dose Ara-C. Although the results showed that LFS did not differ significantly among groups, a subsequent analysis[22] indicated that outcomes of patients with favorable cytogenetic

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markers were significantly better after ASCT or allo-HSCT than after chemotherapy alone, whereas outcomes of patients with unfavorable cytogenetic markers were better after allo-HSCT.

More recent randomized studies have highlighted the advantages of ASCT. A prospective, randomized phase 3 trial carried out by the Dutch–Belgian (HOVON) and Swiss Group (SAKK)[23] compared ASCT with intensive consolidation chemotherapy in AML patients in CR1. Patients who underwent ASCT showed a markedly reduced RI (58% vs 70%, $P=0.02$) and had increased LFS at 5 years (38% vs 29%, $P=0.065$).

Retrospective studies from the EBMT[24,25] and CIBMTR (Center for International Blood and Marrow Transplantation Research)[26] have reported a long-term LFS of ~50% for AML patients who underwent ASCT in CR1 and ~30% in CR2. The CIBMTR[26] concluded that, in the absence of a matched sibling donor, ASCT may be an acceptable post-remission therapy in CR1.

Finally, the quality of life has been shown to be better preserved post ASCT than post allogeneic transplantation:[2–4] The relative risk of grade 3–4 chronic health conditions in long-term survivors was increased by a factor of 2.65 after ASCT, but by 4.5 after allo-HSCT compared with siblings of the survivors.[3]

### ASCT in acute lymphocytic leukemia

The use of HSCT in adult ALL remains controversial. Although the introduction of more aggressive chemotherapy regimens has reduced the need for allo-HSCT in patients younger than 35 years of age, allo-HSCT remains the standard of care for high-risk patients such as slow remitters, patients who are steroid- or chemotherapy-resistant or older than 35 years of age and patients who relapse after CR1. In this context the role of ASCT is difficult to assess. Experience in the early 1990s demonstrated that ASCT is easier to perform in ALL than in AML because of rapid engraftment. TBI was recommended in the pretransplant regimen, and some investigators proposed the use of maintenance chemotherapy following ASCT.[27]

In the MRC UKALLXII/ECOG 2993[13] study, investigators tested if ASCT may be administered instead of consolidation+maintenance for patients lacking an HLA-identical sibling. The OS was significantly worse in the ASCT compared with chemotherapy arm (37% vs 46% at 5 years, $P=0.03$) leading to conclusion that early ASCT cannot substitute consolidation and maintenance. A recent randomized study of 433 adult standard risk ALL patients showed that LFS at 5 years was significantly better in patients who underwent allo-HSCT compared with ASCT (60% vs 42%, $P=0.01$).[12]

A meta-analysis using data from 13 studies including 2962 patients,[15] excluding $Ph^+$ patients, showed that having a matched sibling donor was associated with increased survival, but only for patients $<35$ years old ($P=0.0003$). No beneficial effect of ASCT compared with chemotherapy was observed in this study.

Some recent studies, however, remain in favor of ASCT; in a limited unicentric series[28] of 79 adolescents with ALL who received a 'total therapy protocol' based on ASCT in CR1 from 1990 to 2009, OS and LFS at 5 years were 63 and 62%. Time to CR $>4$ weeks was the only unfavorable prognostic factor by multivariate analysis. Regarding patients older than 55 years, a recent retrospective EBMT study[29] evaluated 267 patients who underwent reduced-intensity conditioning allo-HSCT and 179 patients who underwent ASCT in CR1. The 2-year OS was 44% for reduced-intensity conditioning allo-HSCT and 57% for ASCT ($P=0.02$), and LFS rates were 34% and 41%, respectively ($P=0.06$). In $Ph^+$ BCR/ABL-positive patients, accumulating evidence suggests good outcomes after ASCT in minimal residual disease (MRD)-negative patients treated with TKI.[30]

## EBMT CHANGES IN PRACTICE OVER TIME

As previously mentioned, the use of ASCT for the treatment of AML and ALL has fallen out of favor. For example, the EBMT database contains 7633 patients who underwent allo-HSCT in 2013, but only 455 patients who underwent ASCT in that year.

Nonetheless, many changes in practice have occurred in the last 10 years, as summarized below.

### New pretransplant conditioning regimens

In ASCT, the combinations of cyclophosphamide/TBI, oral busulfan/cyclophosphamide and oral busulfan/etoposide are traditional conditioning regimen. Cyclophosphamide/TBI and busulfan/cyclophosphamide provide equivalent results in AML,[31] whereas cyclophosphamide/TBI is associated with a lower RI in ALL.

Successful new approaches include the use of IV busulfan to reduce NRM,[32,33] anthracyclines to decrease tumor burden, and modifications of the BCNU, etoposide, aracytine, melphalan (BEAM) regimen, which was initially developed for non-Hodgkin's lymphoma. A retrospective EBMT analysis by Nagler *et al*.[34] of data from 952 patients with AML who received IV busulfan before ASCT reported that OS was 67%, LFS 53% and RI 40% at 2 years. NRM at 2 years was only 7%. Of note, the 2-year LFS and RI did not differ significantly between the 815 patients transplanted in CR1 (52% and 40%, respectively) and the 137 patients transplanted in CR2 (58% and 35%, respectively). Cytogenetic risk classification was a significant prognostic factor, with a 2-year LFS of 63% for the good-risk group, 52% for the intermediate-risk group, and 37% for the poor-risk group ($P=0.01$). The combination IV busulfan/high-dose melphalan was associated with the best OS (75%).

Ferrara *et al.* pioneered the use of idarubicin combined with oral busulfan.[35,36] Using the same regimen, researchers in Nanjing[37] reported recently on 32 AML patients who underwent ASCT in CR1, with only one non-relapse death. Median OS and LFS were not reached at 30 months.

The Fukuoka Transplantation Group[38] analyzed outcomes of 81 AML patients autografted in CR1 between 1989 and 2005. The pretransplant regimen consisted of high-dose busulfan, etoposide and cytarabine combined with G-CSF priming. At a median follow-up of 103 months, the 5-year LFS and OS rates were 64% and 66.4%, respectively. The 5-year LFS according to cytogenetics was 81% for good, 64% for intermediate and 33% for poor risk. Relevant to this study, an EBMT retrospective analysis showed that the use of G-CSF after ASCT is not associated with an increased risk of relapse.[39]

The BEAM regimen has been recently advocated for T-cell ALL by the Russian ALL study group,[40] and treatment with TKI for $Ph^+$ ALL[30] is linked with a considerable improvement in 5-year LFS, from 26% in patients who underwent ASCT from 2001 to 2006 (before the introduction of TKI) to 56% in patients who underwent ASCT from 2007 to 2010.

### *In vivo* purging, MRD quantification and graft quality

In the past decade numerous studies on adults and children with AML or ALL have reported that patients who achieve CR1, with no detectable MRD[41] evaluated after induction or conventional consolidation, have a significantly better outcome compared with MRD-positive patients. It is generally recommended that patients who are MRD-positive should be considered for allo-HSCT.[42,43]

Both leukemic and normal progenitors are CD34+ and can be concomitantly mobilized. The European Organization for Research and Treatment of Cancer reported that high levels of CD34+ cells in leukapheresis products are associated with a higher RI after ASCT in AML.[44] This finding is consistent with that of an EBMT study, in which RI was higher with mobilized peripheral blood versus marrow as the stem cell source[24] and also consistent with a

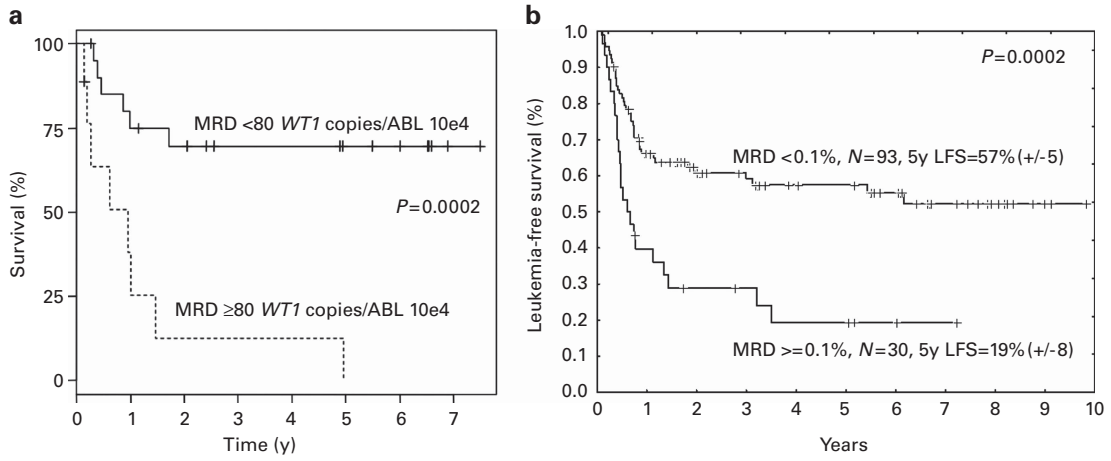


**Figure 1.** The impact of MRD status at time of autologous stem cell transplantation: (**a**) in AML in first remission: Wilms' tumor gene 1 transcript levels in leukapheresis of peripheral blood hematopoietic cells predict relapse risk in patients autografted for acute myeloid leukemia: leukemia-free survival of 30 patients receiving autologous transplantation with apheresis containing $\geqslant 80$ *WT1* copies/ABL 10e4 (dotted line, $n=9$) or $<80$ *WT1* copies/ABL 10e4 (continuous line, $n=21$), $P=0.0002$. From Messina C *et al*. with permission. (**b**) in ALL in first remission: leukemia-free survival after autologous hematopoietic SCT in high-risk Ph-negative adult ALL patients in CR1, according to minimal residual disease (MRD) status at transplantation. From Giebel S *et al.* with permission**.**

subsequent study of 772 patients autografted with leukapheresis products,[25] which reported that relapse was associated with the highest CD34+ cell dose mobilized and infused. The importance of MRD detection by immunophenotyping was demonstrated by the HOVON/SAKK AML 42A study,[45] which reported that high MRD values $>0.1\%$ of blood nucleated cell count were associated with a higher RI in patients with either good- or intermediate-risk cytogenetic markers. In the 54 patients with undetectable MRD consolidated with an autograft, the 4-year RI was 33% and LFS 63%, respectively.

Messina *et al.*[46] evaluated the MRD marker Wilms' tumor gene 1 (*WT1*) by real-time PCR in 30 consecutive patients autografted for AML. A cutoff value of 80 WT1 copies/$10^4$ ABL copies was used to differentiate MRD-positive leukapheresis products. RI was 87% for patients autografted with MRD-positive leukapheresis but only 30% for those transplanted with MRD-negative products ($P=0.0001$) (Figure 1a).

Table 1 summarizes the existing evidence concerning the impact of *in vivo* purging and MRD detection on outcome post ASCT in AML in CR1.

Similar findings have been reported for ALL. The European Study Group for Adult ALL[47] retrospectively analyzed outcomes of 123 patients. In patients with Ph- ALL, the 5-year LFS was higher for those with MRD $<0.1\%$ (57% vs 17%, $P=0.0002$) (Figure 1b). High MRD level was the only independent factor associated with increased risk of failure (risk ratio = 2.8; $P=0.0005$).

These data confirm the original recommendations regarding ASCT. ASCT should be used in chemosensitive patients who have achieved MRD-negative status in the marrow and leukapheresis products.

### Post-transplant maintenance therapy

Post-transplant relapse remains a challenging problem. RI is much higher after ASCT (approaching 45% when done in CR1) than after allo-HSCT, which generates a graft-versus-leukemia effect. The use of post-transplant therapy after ASCT is attractive.[48]

Maintenance therapy post ASCT was introduced in adult ALL by the Royal Marsden team in the UK;[27] of 71 patients in CR 120 days after ASCT, those receiving two or three maintenance agents had significantly lower RI and superior LFS compared with those receiving one or none. In the Russian ALL study group,[40] which used the BEAM regimen in patients with ALL who underwent ASCT in CR1, patients also received maintenance therapy for 2 years post transplant. The 4-year LFS was higher in these patients ($>90\%$) compared with those treated with chemotherapy only (57%). This experience however is limited and needs confirmation.

Results of recent studies suggest the possibility of rescuing AML patients relapsing post allo-HSCT with hypomethylating agents such as 5-azacytidine.[49,50] Low-dose 5-azacytidine induces a CD8+ T-cell response to a variety of tumor Ags.[51] These data may support the use of maintenance therapy post ASCT to reduce relapse incidence.[48]

## PATIENTS WHO MAY BENEFIT FROM ASCT

### A – Good and intermediate-risk patients

Clinical characteristics, used historically to determine risk, include patient age, comorbidities, and response to induction therapy. A first EBMT retrospective study identified age as an important independent prognostic factor.[52] In the more recent study that evaluated patients with AML who received IV busulfan and were autografted in CR1,[34] younger patients ($<50$-year old) had better 2-year OS (77% vs 56%; $P<0.001$), LFS (61% vs 45%; $P<0.001$), RI (35% vs 45%; $P<0.005$) and NRM (4% vs 10%; $P<0.001$) than those older.

Patients who reach cytological CR with only one induction course have a better outcome after ASCT than those who require an additional induction course. The 1991 study of patients with AML autografted in CR1[53] reported a higher LFS for rapid remitters compared with slow remitters (53% vs 42%, $P=0.03$) and this was confirmed in the subsequent analyses.[5,54]

In the past 10 years considerable progress has been made in cytogenetics and molecular biology and the European LeukemiaNet has proposed a standardized reporting for correlation of cytogenetic and molecular genetic data in AML, with the identification of four prognostic groups:[55,56] the 'favorable' group includes patients with either inv(16), t(16;16), t(8; 21), mutated NPM1 without FLT3 ITD (internal tandem duplications) (NPM +/FLT3 ITD – ) or mutated CEBPA. An 'adverse' group consists of patients with inv (3) or t (3;3), t( 6;9), t(v;11) either – 5 or del (5q), – 7, abn (17p) or $\geqslant 3$ cytogenetic abnormalities not including translocations (complex karyotype). An intermediate-1 group comprises patients with a normal karyotype (NK) and with the other genotypic combinations of NPM1 and FLT3 ITD (+/+, – / – , – /+) and an intermediate-2 group consists of patients with t (9;11) and cytogenetic abnormalities not noted above. Importantly,

**Table 1.** Direct and indirect evidence concerning the impact of *in vivo* purging and MRD detection on outcome post autologous stem cell transplantation in acute myelocytic leukemia in first CR

| *Prognostic factor tested at time of ASCT* | *Results* | *Conclusion* | *Interpretation* | *Reference* |
|---|---|---|---|---|
| Number of consolidation courses pre marrow harvest | Administration of two or more courses of consolidation chemotherapy prior to marrow harvest was found the most significant factor associated with decreased RI (RR 2.62, $P=0.0012$) and improved LFS (RR 3.03, $P=0.0009$). | Adequate consolidation of CR before ABMT is the most important factor associated with continuing CR after ABMT. | Importance of adequate *in vivo* purging. | Mehta J *et al.*[82] |
| Number of consolidation courses pre LK | Patients receiving LK collected after a minimum of two chemotherapy courses had a lower RI (20% vs 62%, $P=0.008$) and a better LFS (69% vs 35%, $P=0.02$) than patients receiving LK collected after only one chemotherapy course. | Two consolidation courses mandatory before LK. | Early LK after induction or only one consolidation course may contain residual tumor and/or reflect non achievement of MRD negativity. | Gorin NC *et al.*[5] |
| CD34+ cell dose infused with LK | A high CD34% in LK from 71 AML patients was associated with a high RI ($P=0.006$) and inversely with LFS ($P=0.003$). The RI at 12 months was 67% in a group with $>0.8\%$ CD34+ cells and 34% in a group with $\leqslant 0.8\%$ CD34+ cells. | Higher yields correspond to the presence of mobilized leukemic cells. | Mobilization for LK also mobilize leukemic cells. Importance of MRD monitoring. | Feller N *et al.*[44] |
| CD34+ cell dose infused with LK | RI was more probable in patients who received the highest CD34+ dose ($>7.16\times10(6)$/kg; $P=0.005$), and LFS was worse ($P=0.01$). | Higher yields correspond to the presence of mobilized leukemic cells. | Mobilization for LK also mobilize tumor cells. Importance of *in vivo* purging and MRD monitoring. | Gorin NC *et al.*[25] |
| CD34+/CD38-cell dose infused with LK | Three-year EFS: 62% if CD34+/CD38- population $<0.9\%$ vs 10% if $>10\%$. | Higher yields correspond to the presence of mobilized leukemic cells. | Mobilization for LK also mobilize tumor cells. Importance of *in vivo* purging and MRD monitoring | Plesa A *et al.*[83] |
| Multicolor immunophenotype HOVON/SAAK AML 42A study | Patients autografted with negative MRD have good outcome: 4-year EFS 63%. RI: 33%. | Detection of no residual MRD is associated with excellent outcome. | ASCT as high dose consolidation at time of CR with no MRD detectable produce good results. | Terwijn M *et al.*[45] Cornelissen JJ *et al.*[69] |
| WT1 level: EFS of 30 patients receiving ASCT with LK containing $\geqslant 80$ WT1 copies/ABL 10e4 (group A) or $<80$ copies (Group B) | The RI was 87% in group A and 30% in group B ($P=0.0001$). One-year LFS were 25% for group A and 75% for group B, respectively. | Detection of no residual MRD is associated with excellent outcome. | ASCT as high dose consolidation at time of CR with no MRD detectable may produce the best results. | Messina C *et al.*[46] |

Abbreviations: ABMT= autologous bone marrow transplantation; ASCT = autologous stem cell transplantation; EFS = event-free survival; LFS = leukemia-free survival; LK = leukaphereses; MRD = minimal residual disease; RI = incidence of relapse; RR= relative risk.

recent data have shown that only patients with double CEBPA mutations belong to the 'favorable best group,' with single CEBPA mutations considered as intermediate-1,[57–59] and that the adverse prognostic value of the FLT3 ITD relies strongly to the mutant to wild-type ratio.[60] Also, the favorable effect of NPM1 mutations has been questioned in relation with co-occuring IDH1 or IDH2 mutations.[61–63] The 2012 ELN consensus statement on allogeneic HSCT for patients with AML in remission[64] has been to offer allogeneic hematopoietic cell transplant in the adverse and intermediate groups in whom the RI within 1–2 years post conventional chemotherapy are $\geqslant 90\%$ and 70–80%, respectively, but not to the favorable group, whereas intermediate-1 risk patients have remained in the gray zone. There are indications that patients in the favorable group who still have a RI post conventional chemotherapy around 35–40% and potentially patients in the intermediate-1 risk group with a RI $\sim$50–60% may indeed represent the best candidates for consolidation with ASCT. However, this area remains controversial in the absence of very recent randomized studies comparing ASCT with conventional chemotherapy in the new era of molecular biology and integrated genetic profiling. Some observations may favor this speculative approach:

1. As previously mentioned, the analysis of the 1998 US intergroup study[17] by cytogenetics[22] showed that patients with favorable cytogenetics did significantly better after ASCT or allo-HSCT than after chemotherapy. However, this comparison was based on small sample sizes and results of chemotherapy were rather poor in this favorable risk group when compared with other reports.
2. In an EBMT retrospective study of 325 adult patients autografted in CR1,[65] patients with inv16 who underwent allo-HSCT or ASCT had 5-year LFS of 59% and 66%. Patients with t(8;21) who underwent allo-HSCT or ASCT had 5-year LFS of 60% and 66%, respectively. As expected, NRM was lower and RI higher after ASCT. Both modalities produced identical good outcomes. Unfortunately, no comparison was available in this retrospective study with conventional chemotherapy. Other earlier studies have, however, reported in CBF AML a 5-year OS $\sim$50% with conventional chemotherapy,[66,67] higher RI in t(8;21) than inv(16) and in t(8;21) with a high white blood cell count at diagnosis[68] and for some of these studies, no difference in survival with or without transplantation.[69] Yet, the high RI in these so called 'good risk' patients remains a challenge, which supports attempts at high dose consolidation of CR using ASCT.

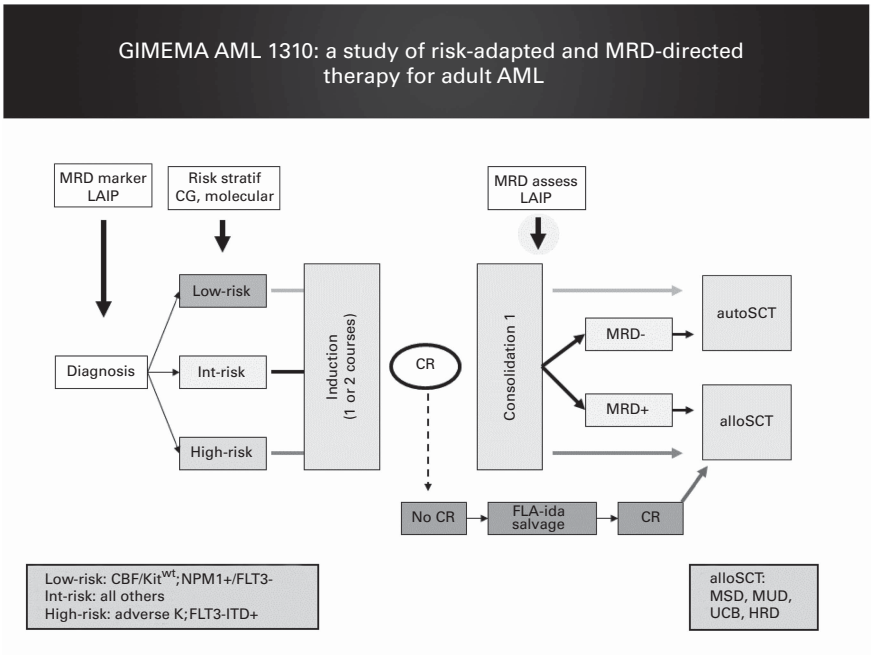


**Figure 2.** The GIMEMA 1310 study: example of a therapeutic protocol tailored for patients with acute myelocytic leukemia based on the evaluation of minimal residual disease. Allo-HSCT = allogeneic hematopoietic stem cell transplantation; ASCT = autologous stem cell transplantation; CG = cytogenetics; HRD = haploidentical related donor; LAIP = leukemia-associated immunophenotype; MRD = minimal residual disease; MUD = matched unrelated donor; UCB = umbilical cord blood. From Venditti A *et al.* with permission. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

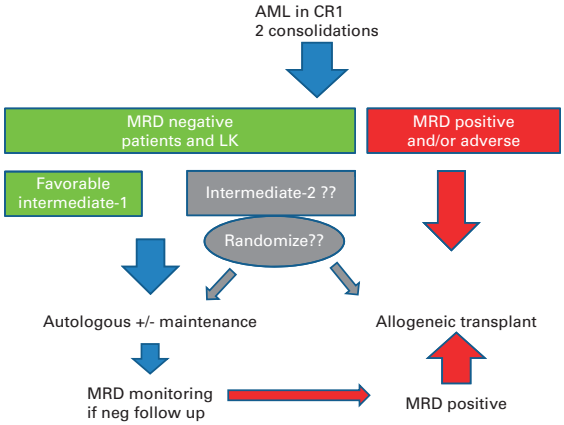


**Figure 3.** Proposal for a simple decision tree for transplant allocation to adult patients with. AML in relation to the Minimal Residual Disease status and the ELN LeukemiaNet prognostic classification.

3. Of considerable interest was the more recent study conducted by Schlenk *et al.*,[70] which among 2983 patients analyzed for CEBPA mutational status (age 18–60 years) treated on four published HOVON/SAKK and three German–Austrian AML Study Group (AMLSG) protocols identified 124 patients with double mutant CEBPA (CEPBAdm) who achieved first CR. Evaluation of the clinical impact of allogeneic and ASCT versus chemotherapy was performed by addressing time dependency in the statistical analyses. Thirty-two patients proceeded to allogeneic transplantation, 20 to ASCT in CR1 and 72 received chemotherapy. Relapse-free survival was significantly superior in patients receiving an allogeneic or an autologous transplant in CR1 as compared with chemotherapy ($P < 0.001$), whereas OS was not different ($P < 0.12$). They concluded that adult AML patients with CEBPAdm benefit from allogeneic and autologous transplants; relapsed patients still had a favorable outcome after reinduction followed by allo-HSCT.
4. Finally, The Hovon group, as already mentionned[71] recently reported results of a time-dependent multivariable analysis of allo-HSCT versus chemotherapy or ASCT in 760 patients with AML in CR1. They concluded that ASCT remains a treatment option in patients with intermediate-risk AML.

Taken together, these findings indicate that ASCT is a therapeutic options for good-risk and possibly intermediate-1 risk AML patients who have reached MRD negativity in marrow and leukapheresis products.

Adult ALL has been traditionally divided into three categories: standard risk, high risk and very high risk. Philadelphia-positive ALL was considered very high-risk. In recent years, it was demonstrated that patients with negative MRD status have a good prognosis regardless of conventional risk factors.[72] It may be hypothesized that patients MRD-negative, who should not be considered candidates for allo-HSCT, could benefit from ASCT; a study evaluating ASCT in patients with ALL is being conducted by the Polish Adult Leukemia Group.

For patients with Ph$^+$ leukemia, recent studies reporting the benefits of ASCT in MRD-negative patients are presented below.

B – Patients who achieve CR with undectable MRD; the proof of concept

Treatment of adult Ph$^+$ ALL and AML M3 in CR2 provide proof-of-concept for ASCT in acute leukemia.

In ALL Ph+, since the introduction of TKI, ASCT has been associated with improved outcome. The Alliance study[73] tested whether imatinib plus sequential chemotherapy would enhance cytoreduction to reduce residual BCR/ABL1-positive lymphoblasts and RI in patients $< 60$ years of age without sibling donors. Patients who underwent ASCT and those who underwent allo-HSCT showed similar OS (median 6.0 years vs not reached) and LFS (median 3.5 vs 4.1 years).

**Table 2.** Suggestions for ASCT in patients with AML

| *Disease and status ELN prognostic*[a] | *Status* | *EBMT assessment* | *Clinical trials needed* | *Additional option* |
|---|---|---|---|---|
| AML favorable in general | CR1 MRD-negative | Therapeutic option | Randomized studies of ASCT vs chemotherapy only | Maintenance vs no maintenance post ASCT |
| AML intermediate-1 in general, any age | CR1 MRD-negative | Therapeutic option | Randomized studies of ASCT vs allo-HSCT (RIC for older fit patients) | Maintenance vs no maintenance post ASCT |
| AML adverse in general | MRD-negative or MRD-positive | Not recommended | | |
| AML favorable and intermediate-1 | CR2 MRD-negative | Therapeutic option | Randomized studies of ASCT vs RIC allo-HSCT | (1) Maintenance vs no maintenance post ASCT (2) targeted therapy to achieve MRD negativity |
| AML M3 | CR2 MRD-negative | Standard of care? | | |
| ALL $Ph^+$/BCR-ABL-positive | CR2 MRD-negative | Standard of care? | | |
| ALL Ph-/BCR-ABL-negative >35-year old, no genoidentical donor | CR1 MRD-negative | Clinical trial | Phase 2: blinatumomab or CAR T cells to achieve MRD negativity and/or as maintenance post ASCT | |

Abbreviations: Allo-HSCT = allogeneic hematopoietic stem cell transplantation; ASCT = autologous stem cell transplantation; EBMT = European Society for Blood and Marrow Transplantation; MRD = minimal residual disease; RIC = reduced-intensity conditioning. [a]According to the European LeukemiaNet.[55,56]

An EBMT retrospective study[30] reported that outcomes after ASCT for Ph+ ALL have improved significantly. For example, 3-year LFS increased from 11% for transplants performed between 1996 and 2001 to 39% between 2002 and 2006 and 52% between 2007 and 2010 ($P < 0.0001$). RI decreased from 70 to 45% and 45% ($P = 0.01$), and NRM was 19, 15 and 3% ($P = 0.08$). In a subgroup of 22 patients treated with TKI and in complete molecular remission at the time of ASCT, the 3-year LFS rate was 65%.

A recent EBMT study compared ASCT with haploidentical allo-HSCT[74] in patients with no genoidentical donor; LFS was higher in the 36 adult patients with $Ph^+$ ALL who underwent ASCT compared with the 17 patients who underwent haploidentical transplant (60% vs 26%, $P = 0.005$). These results may indicate that adult patients with $Ph^+$ ALL who achieve MRD negativity with chemotherapy and TKI should be considered for ASCT in CR1 if they lack a genoidentical donor or are older than 35 years.

In M3 AML, the introduction of all-trans retinoic acid and arsenic trioxide combined with chemotherapy resulted in the cure of ~85% of patients; there is no indication for HSCT in CR1.[75] For the 15% patients who relapse, ASCT with PML-RAR-negative cells is a therapeutic option in CR2.[76–78]

In the largest case series reported recently, CIBMTR[79] reviewed 294 patients with M3 AML treated with allo-HSCT ($n = 232$) or ASCT ($n = 62$). Multivariate analysis showed that, compared with allo-HSCT, ASCT was associated with higher LFS (63% vs 50%, $P = 0.01$) and OS (75% vs 54%, $P = 0.0006$) at 5 years. The survival advantage was attributed to increased NRM in the allo-HSCT group (30%) compared with the ASCT group (2%).

The Japan Adult Leukemia Study Group[80] reported results of a phase 2 study of arsenic trioxide followed by ASCT for relapsed M3 AML. Of 35 patients, 23 underwent ASCT with PML-RARα-negative cells; the 5-year event-free survival and OS were 65% and 77%, respectively. However, arsenic trioxide exposure before CD34+ cell harvest may have deleterious effects on hematopoietic recovery after ASCT.[81]

Taken together, these data indicate that adult $Ph^+$ ALL and M3 AML in CR2 may represent niche indications for ASCT, providing proof of concept for the use of MRD-negative leukapheresis products. Whether this treatment is appropriate for all MRD-negative patients with acute leukemia in CR1 (or possibly CR2) warrants attention in future randomized studies.

Some national groups have already developed risk adapted and MRD directed therapeutic protocols such as the Italian GIMEMA AML 1310 (Figure 2). Figure 3 proposes a simple decision tree for patients with AML in CR1.

Table 2 gives suggestions for ASCT in adult AML and ALL.

C – Combining tools: the potential impact of new targeted therapies

A number of targeted therapies are currently tested for AML and ALL. These include epigenetic therapy, monoclonal antibodies, bispecific monoclonal antibodies and chimeric Ag receptor T cells. Any of these agents could be added to ASCT, at any step of the procedure. For example, administration of the targeted therapy before stem cell collection may help patients to achieve MRD negativity and/or administration after ASCT may be useful as post-transplant maintenance therapy.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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NCG wrote the first draft of the paper. SG, ML, BS, MM and AN all contributed to and approved the final version.

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