Remission induction versus immediate allogeneic haematopoietic stem cell transplantation for patients with relapsed or poor responsive acute myeloid leukaemia (ASAP): a randomised, open-label, phase 3, non-inferiority trial

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Summary

Background Whether high-dose cytarabine-based salvage chemotherapy, administered to induce complete remission in patients with poor responsive or relapsed acute myeloid leukaemia scheduled for allogeneic haematopoietic stem-cell transplantation (HSCT) after intensive conditioning confers a survival advantage, is unclear.

Methods To test salvage chemotherapy before allogeneic HSCT, patients aged between 18 and 75 years with non-favourable-risk acute myeloid leukaemia not in complete remission after first induction or untreated first relapse were randomly assigned 1:1 to remission induction with high-dose cytarabine (3 g/m² intravenously, 1 g/m² intravenously for patients >60 years or with a substantial comorbidity) twice daily on days 1–3 plus mitoxantrone (10 mg/m² intravenously) on days 3–5 or immediate allogeneic HSCT for the disease control group. Block randomisation with variable block lengths was used and patients were stratified by age, acute myeloid leukaemia risk, and disease status. The study was open label. The primary endpoint was treatment success, defined as complete remission on day 56 after allogeneic HSCT, with the aim to show non-inferiority for disease control compared with remission induction with a non-inferiority-margin of 5% and one-sided type 1 error of 2·5%. The primary endpoint was analysed in both the intention-to-treat (ITT) population and in the per-protocol population. The trial is completed and was registered at ClinicalTrials.gov, NCT02461537.

Findings 281 patients were enrolled between Sept 17, 2015, and Jan 12, 2022. Of 140 patients randomly assigned to disease control, 135 (96%) proceeded to allogeneic HSCT, 97 (69%) after watchful waiting only. Of 141 patients randomly assigned to remission induction, 134 (95%) received salvage chemotherapy and 128 (91%) patients subsequently proceeded to allogeneic HSCT. In the ITT population, treatment success was observed in 116 (83%) of 140 patients in the disease control group versus 112 (79%) of 141 patients with remission induction (test for non-inferiority, p=0·036). Among per-protocol treated patients, treatment success was observed in 116 (84%) of 138 patients with disease control versus 109 (81%) of 134 patients in the remission induction group (test for non-inferiority, p=0·047). The difference in treatment success between disease control and remission induction was estimated as 3·4% (95% CI −5·8 to 12·6) for the ITT population and 2·7% (−6·3 to 11·8) for the per-protocol population. Fewer patients with disease control compared with remission induction had non-haematological adverse events grade 3 or worse (30 [21%] of 140 patients *vs* 86 [61%] of 141 patients, χ^2 test p<0·0001). Between randomisation and the start of conditioning, with disease control two patients died from progressive acute myeloid leukaemia and zero from treatment-related complications, and with remission induction two patients died from progressive acute myeloid leukaemia and two from treatment-related complications. Between randomisation and allogeneic HSCT, patients with disease control spent a median of 27 days less in hospital than those with remission induction, ie, the median time in hospital was 15 days (range 7–64) versus 42 days (27–121, U test p<0·0001), respectively.

Interpretation Non-inferiority of disease control could not be shown at the 2·5% significance level. The rate of treatment success was also not statistically better for patients with remission induction. Watchful waiting and immediate transplantation could be an alternative for fit patients with poor response or relapsed acute myeloid leukaemia who have a stem cell donor available. More randomised controlled intention-to-transplant trials are needed to define the optimal treatment before transplantation for patients with active acute myeloid leukaemia.

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See Online for appendix

Introduction

For patients with relapsed acute myeloid leukaemia or induction failure, allogeneic haematopoietic stem-cell transplantation (HSCT) is the treatment with the best chances for long-term leukaemia-free survival.

Advances in stem cell donor selection, graft-versus-host disease prophylaxis, conditioning regimens, and supportive care have led to substantial improvements in survival.[1–4] Although very few prospective studies have tested the effect of interventions before allogeneic HSCT,

Research in context

Evidence before this study

Patients with non-favourable risk acute myeloid leukaemia and a delayed response to intensive induction chemotherapy or relapsed acute myeloid leukaemia are candidates for allogeneic haematopoietic stem cell transplantation (HSCT).
As observational studies suggest superior outcomes for patients who reach complete remission before allogeneic HSCT, remission induction chemotherapy before allogeneic HSCT is considered the standard of care for most of these patients. However, salvage chemotherapy often does not lead to complete remission and can result in complications that prevent subsequent allogeneic HSCT. Moreover, a survival advantage of the remission induction strategy has never been proven in a prospective randomised trial. We did several literature searches, last on March 22, 2024, using key search terms including randomized controlled trial, allogeneic stem cell transplantation, aml, and remission induction. We did not find any relevant studies on the value of remission induction before allogeneic HSCT in a randomised setting.

Added value of this study

Motivated by data from retrospective studies and prospective phase 2 studies, which showed promising outcomes for patients not in complete remission treated with intensive conditioning and immediate allogeneic HSCT, we questioned the current standard to induce complete remission with salvage chemotherapy before allogeneic HSCT. Our key hypothesis was that salvage chemotherapy would not provide a net benefit for patients with acute myeloid leukaemia with a poor response to intensive induction therapy or relapsed disease when compared with immediate allogeneic HSCT after intensive conditioning. To test this hypothesis, we randomly assigned patients to receive either salvage chemotherapy with high-dose cytarabine plus mitoxantrone with the aim to induce a complete remission first or to proceed immediately to allogeneic HSCT. Patients randomly assigned to immediate allogeneic HSCT were kept preferentially on watchful waiting without any anti-leukaemic therapy before allogeneic HSCT. We could not show non-inferiority of immediate allogeneic HSCT at the pre-specified one-sided 2·5% significance level, but the results also showed no benefit of salvage chemotherapy. Yet, patients spent 1 month longer in hospital with salvage chemotherapy before allogeneic HSCT and had more adverse events than those treated with immediate allogeneic HSCT.

The ASAP trial was a first in its kind randomised trial evaluating a benefit of salvage treatment for acute myeloid leukaemia before allogeneic HSCT. Given the absence of evidence from prospective controlled trials in favour of complete remission induction before allogeneic HSCT, data from the ASAP trial are remarkable. The rate of treatment success in the per-protocol population, defined as complete remission at day 56 after allogeneic HSCT, was estimated as 2·7% (95% CI –6·3% to 11·8%) for disease control versus remission induction. Yet, the crucial lower range of the 95% CI for non-inferiority testing was –6·3% instead of –5·0%, the pre-specified non-inferiority margin. Thus, on one hand, non-inferiority of immediate transplantation was not shown within pre-defined limits but on the other hand, the current standard of salvage chemotherapy before allogeneic HSCT was not supported by the results either. Conceptually, results of the ASAP trial suggest that predominantly acute myeloid leukaemia biology and not the tumour load determines the prognosis after allogeneic HSCT.

Implications of all the available evidence

One conclusion is that more efforts have to be made to show the benefit of treatment interventions before allogeneic HSCT, which aim at improving outcomes after allogeneic HSCT. Randomised controlled trials are the only proper way to show an advantage of potentially costly and toxic treatment interventions before allogeneic HSCT. For patients with relapsed or refractory acute myeloid leukaemia with *FLT3*–ITD–TKD mutations, chemotherapy was inferior to the tyrosine kinase inhibitor gilteritinib in the randomised registration trial. Outcomes were most promising for patients, who proceeded to allogeneic HSCT and continued with gilteritinib maintenance after transplantation. With the approval of *FLT3*-inhibitors, treatment with these targeted drugs before allogeneic HSCT is a very attractive option for this subgroup of patients. More randomised controlled trials are necessary to define the optimal dose-intensity of conditioning regimens for well defined disease stages ranging from untreated active acute myeloid leukaemia to measurable residual disease negative disease stages.

When carefully weighing all available evidence, immediate allogeneic HSCT after intensive conditioning could be offered as an alternative path to long-term disease control for patients with relapsed or refractory acute myeloid leukaemia who are most suitable for such an approach. These patients include those with *FLT3* wildtype, non-hyperproliferative acute myeloid leukaemia, who are fit, both physically and medically, and who have a stem cell donor readily available.

numerous retrospective studies have reported that patients in complete remission have better survival chances after allogeneic HSCT than patients with residual acute myeloid leukaemia.[5,6] Most of these studies, however, did not account for the underlying molecular risk profile and—even more importantly—did not report on the selection process before transplantation. Albeit never shown in a randomised trial, attempting to induce complete remission before allogeneic HSCT is standard of care and in many centres, complete remission is even considered as a gateway to transplantation.

To avoid clonal evolution of acute myeloid leukaemia and reduce toxicity, transplantation strategies for patients with poor chances of reaching complete remission have been developed, including allogeneic HSCT in aplasia immediately after induction chemotherapy[7–9] as well as sequential conditioning regimens for patients with active disease.[10–14] Promising results of these sequential conditioning regimens prompted us to ask whether patients with active acute myeloid leukaemia, who are scheduled for allogeneic HSCT and have an HLA-compatible stem cell donor available, would benefit from an attempt to induce a complete remission. Therefore, we aimed to conduct a prospective randomised trial comparing disease control measures and immediate allogeneic HSCT with the standard approach of salvage chemotherapy to induce complete remission before allogeneic HSCT.

Methods

Study design and participants

The ASAP trial[15] was a multicentre, open label, randomised controlled trial testing non-inferiority of immediate allogeneic HSCT compared with salvage chemotherapy intended to induce complete remission followed by allogeneic HSCT. 16 centres spread across Germany were involved in the trial (appendix p 4). The Institutional Review Board of TU Dresden (IRB00001473) and the German Federal Institute for Drugs and Medical Devices approved the trial. An independent Data Monitoring Committee reviewed safety data and trial conduct in April 2018, April 2019, June 2020, May 2021, and February 2022. The trial was conducted according to the International Council for Harmonisation Good Clinical Practice Guidelines and the principles of the declaration of Helsinki. Five protocol versions were implemented by amendments, introducing changes of eligibility criteria (Jan 22, 2016, version 3.0, Jan 19, 2017, version 4.0, and April 15, 2019, version 5.0), specification of processes and administrative changes (Feb 27, 2015, version 2.0, Jan 22, 2016, version 3.0, Jan 19, 2017, version 4.0, and April 15, 2019, version 5.0), ancillary research and safety reporting processes (Jan 22, 2016, version 3.0), changes in stratification (April 15, 2019, version 5.0), and the specification of the process of study termination after observation of the crucial number of patients in the per-protocol population (Feb 22, 2022, version 6.0).

We enrolled patients aged 18–75 years with either first untreated relapse of acute myeloid leukaemia or poorly responsive acute myeloid leukaemia, as defined by 5% or higher marrow blasts after the first course of induction chemotherapy in the context of non-favourable risk genetics according to the European Leukemia Network (ELN) 2010.[16] To rule out that patients who had a poor response after first induction containing high-dose cytarabine would be re-exposed with high-dose cytarabine during salvage chemotherapy, patients with poor response after cytarabine at doses of more than 1 g/m² were not eligible. Patient had to be fit for intensive salvage chemotherapy as assessed by a senior haematologist. Availability of an HLA-compatible related or unrelated donor (≥9 of 10 alleles matched for HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1) had to be ensured at randomisation, either by confirmatory typing or by more than 90% probability for two compatible unrelated donors. Patients with white blood cell counts of more than 50×10^9 cells per L, central nervous system manifestations, or a history of allogeneic HSCT were excluded, as were patients with a cumulative exposure to more than 440 mg/m² daunorubicin equivalents, a left ventricular ejection fraction of less than 50%, a need for oxygen supplementation, a bilirubin concentration of more than 1·5 times the upper limit of normal, or a glomerular filtration rate of less than 50 mL/min. A full list of inclusion and exclusion criteria is provided in the appendix (pp 5–6). All patients gave written informed consent.

Randomisation and masking

Patients were randomly assigned 1:1 to remission induction or disease control before allogeneic HSCT using block randomisation with variable block lengths. We stratified randomisation by age (ie, 60 years or younger *vs* older than 60 years), acute myeloid leukaemia risk defined by ELN 2010 criteria, and by a history of cancer treatment or an antecedent haematological malignancy and disease status (poor response after first induction or first untreated haematological relapse).[16] Randomisation lists for all risk strata were computer-generated by an external statistician and imported into the clinical database system. The database was hosted by a third party. Randomisation lists could not be accessed by trial staff. Trial sites received information on patient allocation after entering baseline data on individual, eligible patients. Study treatment was open label and staff who performed study assessments were not blinded. Aggregated data on treatment allocation and outcome by study group could not be accessed by the study statistician or researchers before the data base was locked.

Procedures

In the disease control group, patients proceeded to allogeneic HSCT as soon as possible. Patients were allowed to receive low dose cytarabine or single doses of

mitoxantrone 10 mg/m² intravenously. Subsequently, all patients were scheduled for sequential conditioning consisting of intensive chemotherapy followed by reduced-intensity conditioning. FLAMSA-reduced-intensity conditioning consisted of fludarabine, amsacrine, and cytarabine on days –12 to –9 followed by fludarabine-alkylator-based reduced intensity conditioning before transplantation. Melphalan–fludarabine and total body irradiation consisted of high-dose melphalan on day –11 combined with fludarabine plus cumulative total body irradiation with 8 Gray before allogeneic HSCT. Graft-versus-host disease prophylaxis was based on anti-thymocyte globulin, cyclosporine, and mycophenolate mofetil.

In the remission induction group, salvage chemotherapy consisted of high dose cytarabine 3 g/m² intravenously (1 g/m² intravenously for patients >60 years or with substantial comorbidity) twice daily on days 1–3 and mitoxantrone 10 mg/m² intravenously on days 3–5 (HAM). One course of salvage chemotherapy was administered. After remission assessment, patients were referred for allogeneic HSCT regardless of the remission status. Conditioning intensity was tailored to the level of residual disease and the patient's condition.

The following study assessments were implemented at baseline, response evaluation after HAM (for the remission induction group only), allogeneic HSCT, and final remission assessment up to day 56 after allogeneic HSCT: blood tests, bone marrow aspirate or histology, adverse events, and Eastern Cooperative Oncology Group performance status. In addition, items for the calculation of the Haematopoietic Cell Transplantation-specific Comorbidity Index were assessed at baseline and before allogeneic HSCT. Annually after randomisation, remission status, Eastern Cooperative Oncology Group performance status, and graft-versus-host disease status were assessed. Patients had the right to withdraw from the trial at any time and for any reason. Additionally, patients discontinued the study treatment if they became ineligible for allogeneic HSCT according to investigator's assessment. Further information on conditioning regimens and graft-versus-host disease prophylaxis is provided in the appendix (pp 8–9).

A binary definition of sex was used and self-reported assignment into male or female sex was used for patients and donors. For the final analysis, available information (ie, karyotype, *CEBPA*, *NPM1*, and *FLT3*-mutation status) was reclassified according to ELN 2022 definitions.[17] Complete remission was defined by bone marrow blasts less than 5% or bone marrow donor chimerism more than 95% and absence of extramedullary disease plus haematopoietic recovery defined by neutrophil counts of more than 1×10^9 cells per L and platelet counts of more than 100×10^9 platelets per L or complete remission with incomplete count recovery according to ELN. Relapse or progression during follow-up was defined as bone marrow blasts 5% or more, reappearance of blasts in the peripheral blood, development of extramedullary disease, or reappearance of measurable residual disease defined by a suitable molecular marker in two subsequent samples. Adverse events were collected from randomisation until day 28 after the last dose of study treatment or the start of subsequent anti-leukaemic treatment and conditioning. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). Time in hospital before allogeneic HSCT was calculated for the per-protocol population who underwent transplantation as the total number of overnight stays between randomisation and allogeneic HSCT, and the time to discharge after allogeneic HSCT was the total number of overnight stays between allogeneic HSCT and day of discharge, also for the per-protocol population who underwent transplantation.

Outcomes

The primary endpoint of this intention-to-transplant study was the rate of treatment success, defined as documented complete remission on day 56 after allogeneic HSCT. Treatment success was anchored to allogeneic HSCT for three reasons: first, the critical treatment step towards long-term disease control for patients with high-risk acute myeloid leukaemia is allogeneic HSCT; second, allogeneic HSCT entails greater risk of non-relapse mortality than salvage chemotherapy (a timescale starting at allogeneic HSCT thus allows for a better comparison of outcomes than a timescale starting at randomisation); and third, being alive and in complete remission after allogeneic HSCT is a necessary condition for long-term survival. Treatment success had to be assessed no later than 24 weeks from randomisation. Any outcome not meeting the criteria of treatment success was counted as treatment failure, eg, death before transplantation, withdrawal of consent, deferred allogeneic HSCT, no complete remission after allogeneic HSCT, or early relapse within 56 days after allogeneic HSCT. Overall survival from randomisation was pre-specified as a major secondary endpoint to describe mortality at 4 weeks, 8 weeks, and 24 weeks from randomisation and during follow-up. Additional secondary endpoints were the cumulative incidences of allogeneic HSCT, complete remission at 4 weeks, 8 weeks, and 24 weeks from randomisation. We estimated leukemia-free survival from final remission assessment after allogeneic HSCT, ie, at day 56 after allogeneic HSCT, with relapse or death as composite endpoints. Detailed definitions of the primary and major secondary endpoints are shown in the appendix (p 7). In patients treated with remission induction, we analysed the complete remission rate after HAM. Further, we analysed overall survival and event-free survival after allogeneic HSCT and the cumulative incidences of relapse and non-relapse mortality. We complemented these analyses with risk factor analyses to investigate the effect of baseline characteristics at randomisation and at HSCT. Since rates

of allogeneic HSCT were exceptionally high in both groups and allogeneic HSCT was performed substantially earlier with disease control compared with remission induction, we did not investigate the availability of HLA-compatible donors and donor clearance at 4 weeks, 8 weeks, and 16 weeks from randomisation. Time in hospital before allogeneic HSCT, time to discharge after allogeneic HSCT, and graft-versus-host disease and relapse-free survival by study group were added as post-hoc analyses. Events for graft-versus-host disease and relapse free survival were grade 3–4 acute graft-versus-host disease, severe chronic graft-versus-host disease, relapse, or death whichever came first. Cumulative incidences of acute and chronic graft-versus-host disease were assessed as part of the safety analyses according to the protocol.

Statistical analysis

Showing non-inferiority would be sufficient to replace remission induction by disease control for the selected patient population because intensive salvage chemotherapy to induce remission before allogeneic HSCT causes substantial adverse effects, extra time in hospital, and increased costs. The sample size was calculated to show non-inferiority with respect to treatment success on day 56 after allogeneic HSCT with a one-sided type I error of 2·5%, a power of 80%, and a non-inferiority margin of 5% in the per-protocol population. We assumed rates of allogeneic HSCT of 83% and 70% and rates of treatment success of 68% and 55% for the disease control group and remission induction group, respectively. The non-inferiority margin of 5% was consented by the protocol committee based on reasoning that for patients with acute myeloid leukaemia not in complete remission scheduled for allogeneic HSCT risks of that order of magnitude could be acceptable. On the basis of these figures, the trial aimed at the analysis of 246 patients (123 per group) in the per-protocol population. To account for an assumed non-compliance rate of 25%, the initial recruitment target was set at 308 patients. The original plan was to enrol the crucial number of patients within 36 months. The trial was stopped after data from more than 246 patients were evaluable in the per-protocol population because the the non-compliance rate turned out to be less than 5%. This lower observed rate of non-compliance reduced the necessary number of patients for the intention-to-treat population. No data were missing to assess treatment success.

The primary endpoint was evaluated as success rate according to Farrington and Manning[18] in the intention-to-treat (ITT) population and in the per-protocol population. Per-protocol treatment was defined by start of salvage chemotherapy with high-dose cytarabine for patients randomly assigned to remission induction and assignment to watch and wait, low-dose cytarabine, or single doses of mitoxantrone for patients randomly assigned to disease control and immediate allogeneic HSCT in the experimental group. The goal was to show non-inferiority with respect to treatment success with a one-sided type I error of 2·5%, a power of 80%, and a non-inferiority margin of 5%. No interim analysis had been performed. The primary efficacy analysis was triggered per protocol after 246 patients were evaluable in the per-protocol population. Secondary endpoints were tested without adjusting for multiplicity with a nominal two-sided type I error of 5%.

Probabilities for time-dependent events were calculated according to Kaplan–Meier and analysed with the log-rank test in univariable comparisons. Incidences of events were estimated with cumulative incidence statistics, considering death as a competing event. Univariable comparisons of cumulative incidences were calculated with the Gray test. Point estimates at defined timepoints were compared by means of a *Z* test. Multivariable logistic regression analyses were fitted for treatment success and Cox regression analyses for overall survival from randomisation. Patient age, patient sex, Eastern Cooperative Oncology Group performance status score, Haematopoietic Cell Transplantation-specific Comorbidity Index score, disease status, ELN risk, and diagnosis were used for risk adjustment. All point estimates are reported together with 95% CIs. Observed rates of adverse events were compared by means of a χ^2 test in the intention-to-treat population. We used IBM SPSS Statistics (version 29.0) and R (version 4.1) for the statistical analysis. The trial was registered with ClinicalTrials.gov (NCT02461537).

Role of the funding source

The study design and trial interventions were defined by academic investigators from the Study Alliance Leukemia and the German Cooperative Transplant Study Group. DKMS financed the trial and provided administrative and regulatory support. Trial coordination, data management, and statistics were covered by the Clinical Trials Unit of DKMS.

Results

Between Sept 17, 2015, and Jan 12, 2022, 281 patients were enrolled (figure 1). The ITT population comprised 281 patients, 183 patients with poor response after a first course of intensive induction chemotherapy and 98 patients with first untreated relapse of acute myeloid leukaemia. The per-protocol population consisted of 272 patients.

At randomisation, the median age of all ITT patients was 61 years (IQR 52–66 years, range 18–75 years; table 1). The Hematopoietic Cell Transplantation—Comorbidity Index indicated relevant comorbidity (scores ≥3) for 107 (38%) of 281 patients. The median bone marrow blast count at randomisation was 30% (IQR 16–50) in both groups. Reclassification according to ELN 2022 showed a statistically non-significant predominance of patients with adverse risk acute myeloid leukaemia in the poor response acute myeloid leukaemia stratum of the disease control group compared with the remission induction

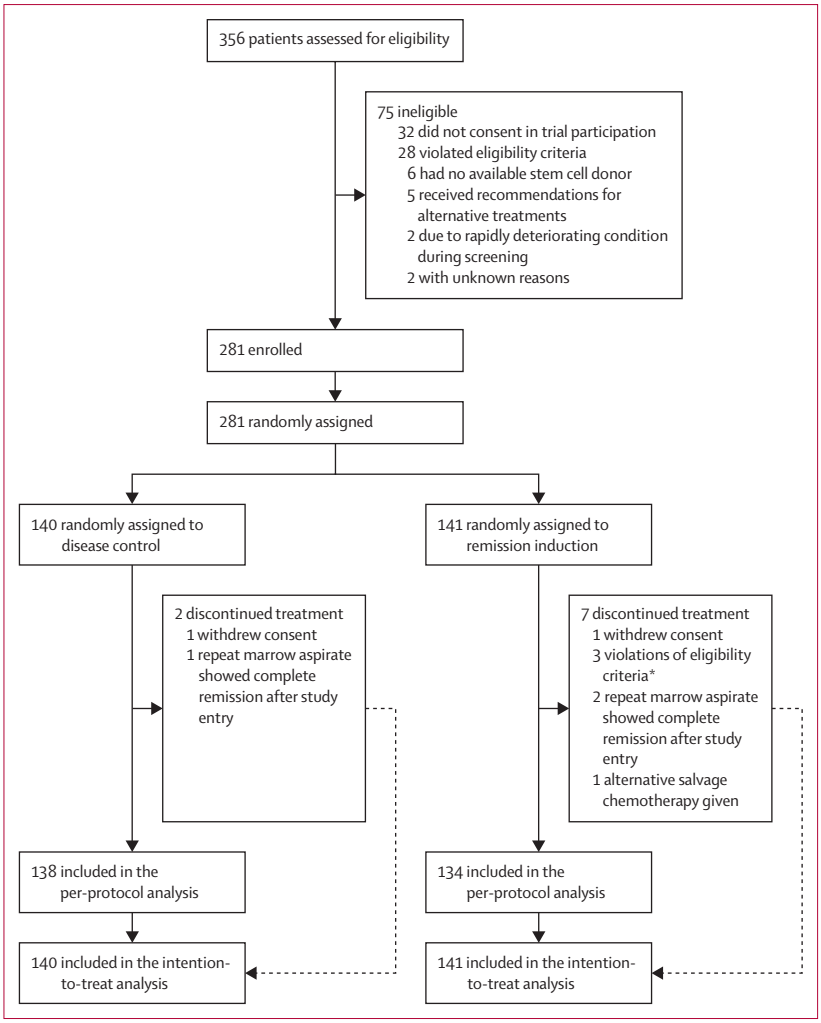

Figure 1: **Trial profile**
*Violations of eligibility criteria that prevented per-protocol treatment consisted of preceding induction therapy, which contained AraC >1g/m² (n=1), left ventricular ejection fraction of <50% (n=1), or overlapping treatment with an investigational drug (n=1).

	Disease control (n=140)	Remission induction (n=141)
Age, years	61 (50–66; 18–75)	61 (54–65; 19–74)
Sex		
Female	64 (46%)	61 (43%)
Male	76 (54%)	80 (57%)
Eastern Co-operative Oncology Group performance status		
0–1	123 (88%)	127 (90%)
2	17 (12%)	14 (10%)
Haematopoietic cell transplantation—comorbidity index	2 (0–3; 0–10)	1 (0–3; 0–8)
Bone marrow blasts	30% (15–50; 2–95)	30% (18–50; 0–90)
Acute myeloid leukaemia type		
de novo	110 (79%)	102 (72%)
Secondary acute myeloid leukaemia	22 (16%)	33 (23%)
Therapy-related acute myeloid leukaemia	8 (6%)	6 (4%)
Disease status		
Poor induction response	90 (64%)	93 (66%)
Relapse	50 (36%)	48 (34%)
Donor search status		
Matched sibling donor	19 (14%)	20 (14%)
Unrelated donor with ≥9 of 10 human leukocyte antigen-compatibility	65 (46%)	72 (51%)
Search ongoing	56 (40%)	49 (35%)
European Leukemia Network 2022		
Favourable	13 (9%)	15 (11%)
Intermediate	79 (56%)	90 (64%)
Adverse	48 (34%)	36 (26%)
European Leukemia Network 2022 among poor responders		
Favourable	1/90 (1%)	1/93 (1%)
Intermediate	44/90 (49%)	61/93 (66%)
Adverse	45/90 (50%)	31/93 (33%)
European Leukemia Network 2022 among relapsed patients		
Favourable	12/50 (24%)	14/48 (29%)
Intermediate	35/50 (70%)	29/48 (60%)
Adverse	3/50 (6%)	5/48 (10%)

Data are median (IQR; range), n (%), or n/N (%). Data on ethnicity were not collected.

Table 1: **Patient characteristics of the intention-to-treat population at baseline**

group (45 [50%] of 90 patients *vs* 31 [33%] of 93 patients, χ^2 p=0·071). Distribution of patient characteristics in the two main strata, relapsed acute myeloid leukaemia and poor response acute myeloid leukaemia, and in the per-protocol population are shown in the appendix (pp 10, 20).

Of 140 patients randomly assigned to disease control, 135 (96%) patients proceeded to allogeneic HSCT; 97 (69%) patients after watchful waiting only and 38 (27%) patients after anti-leukaemic therapy (appendix p 24). Three patients died without allogeneic HSCT, the decision for allogeneic HSCT was revised in one patient, and one patient withdraw from the trial on day 42 after randomisation. In the disease control-group, anti-leukaemic treatment was administered more often to patients with higher peripheral blast counts compared with watchful waiting only (median $0{\cdot}1\times10^9$ blasts per L [IQR $0{\cdot}0–0{\cdot}8\times10^9$ blasts per L] *vs* $0{\cdot}0\times10^9$ blasts per L [$0{\cdot}0–0{\cdot}0\times10^9$ blasts per L]; p=0·0001), higher lactate dehydrogenase (median 252 U/L [IQR 190–366 U/L] *vs* 199 U/L [164–256 U/L]; p=0·013), and extramedullary manifestations (6 [16%] of 38 patients *vs* 1 [1%] of 95 patients; p=0·0017; appendix p 11). Seven (5%) of 140 patients switched to intensive salvage chemotherapy after inefficient disease-control attempts. At 16 weeks from randomisation, 135 (96%) of 140 patients had been transplanted, 114 (84%) of 135 after sequential conditioning. The median time between randomisation and allogeneic HSCT was 4·4 weeks (IQR 3·6–5·9).

Of 141 patients randomly assigned to remission induction, 134 (95%) received the per-protocol salvage

chemotherapy with HAM. Among per-protocol treated patients, three patients younger than 60 years received 1 g/m² cytarabine intravenously instead of 3 g/m², one patient did not receive mitoxantrone inadvertently, and one patient did not receive the last dose of mitroxantrone due to sepsis (appendix pp 21, 25). After salvage chemotherapy, four patients died from toxicity or progressive acute myeloid leukaemia early after salvage chemotherapy (appendix p 18). Two patients did not reach complete remission with salvage chemotherapy, decided against allogeneic HSCT, and died later from acute myeloid leukaemia. 68 (51%) of 134 patients reached complete remission, but two patients relapsed before allogeneic HSCT and one patient died in complete remission. Of 128 patients who proceeded to allogeneic HSCT, 65 (51%) patients were referred for allogeneic HSCT who were in complete remission and 63 (49%) patients who were not in complete remission. Of the latter group, 45 (71%) of 63 patients proceeded to allogeneic HSCT with sequential conditioning, 44 of them without further attempts to induce complete remission. At 16 weeks from randomisation, 124 (93%) of 134 patients had been transplanted. The median time between randomisation and allogeneic HSCT was 7·9 weeks (IQR 7·0–9·1).

Of the ITT population, 116 (83%) of 140 patients in the disease control group compared with 112 (79%) of 141 patients in the remission induction group reached the primary endpoint of complete remission on day 56 after allogeneic HSCT (appendix p 34). Corresponding numbers for the per-protocol population were 116 (84%) of 138 patients in the disease control group compared with 109 (81%) of 134 patients in the remission induction group. The difference in treatment success between disease control and remission induction was estimated as 3·4% (95% CI −5·8 to 12·6) for the ITT population and 2·7% (−6·3 to 11·8) for the per-protocol population. With the non-inferiority margin of 5% the p values for the Farrington Manning tests for non-inferiority were p=0·036 in the ITT population and p=0·047 in the per-protocol populations (appendix p 16). Non-inferiority of disease control compared with remission induction could thus not be shown at the 2·5% significance level for the ITT and per-protocol population (appendix pp 34–35). Subgroup analyses revealed no baseline characteristic associated with worse outcomes for patients randomly assigned to disease control compared with remission induction (appendix p 15). No test for interactions between any baseline characteristic and the study treatment was statistically significant at the two-sided 10% level.

Analysed according to the ITT population, 4-year overall survival from randomisation was 46% (95% CI 36–55) in the disease control group compared with 49% (39–59) in the remission induction group (log-rank test, p=0·42; figure 2; appendix p 16). As of the database lock, 66 deaths were observed in the disease control group compared with 58 deaths in the remission induction group. In a multivariable Cox regression analysis, age, ELN risk, performance status, and the Haematopoietic Cell Transplantation-specific Comorbidity Index predicted survival (appendix p 26). Survival from randomisation for subgroups of patients is shown in the appendix (pp 27–29).

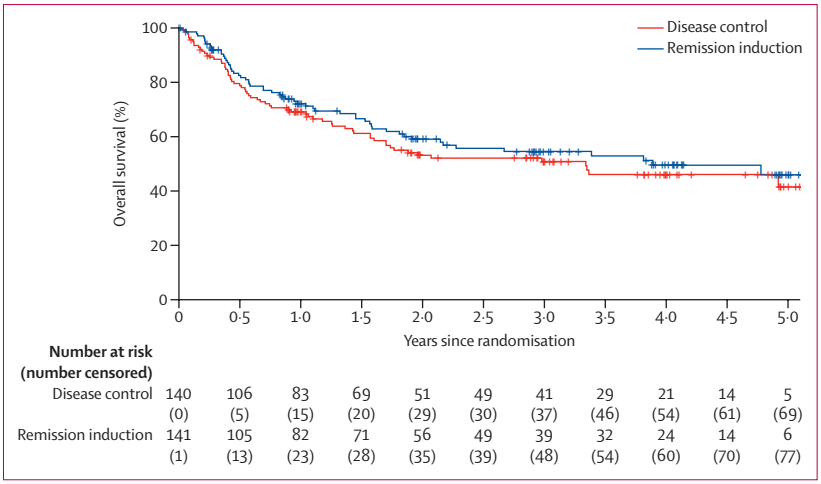

Figure 2: **Overall survival from randomisation according to intention-to-treat**

In the ITT population, cumulative incidences of allogeneic HSCT at 4 weeks and 8 weeks were significantly higher with disease control (41%, 95% CI 33–50 and 91%, 86–96, respectively) compared with remission induction (0% and 53%, 95% CI 45–61) but did not differ significantly at 16 weeks and 24 weeks (appendix p 16). Cumulative incidences of complete remission at 8 weeks, 16 weeks, and 24 weeks from randomisation by study group are reported in the appendix (p 16) as are the times to allogeneic HSCT and times to complete remission by study group for both study groups (p 23). Patient and donor characteristics at admission for allogeneic HSCT of transplanted patients are shown in the appendix (pp 12–14).

With a median follow-up of 37 months (IQR 23–49), 4-year leukaemia-free survival from day 56 in the per-protocol population was 47% (95% CI 36–57) in the disease control group compared with 49% (37–60) in the remission induction group (log-rank test, p=0·50; appendix pp 17, 34–35). Among all transplanted patients, 4-year non-relapse mortality and cumulative incidence of relapse after HCT was 23% (95% CI 16–31) and 36% (27–46) in the disease control group versus 23% (14–31) and 34% (24–44) in the remission induction group, respectively (appendix p 30). Cumulative incidences of non-relapse mortality and relapse after allogeneic HSCT for subgroups of patients are shown in the appendix (pp 30–32).

In the disease control group, 3-year overall survival was 59% (95% CI 48–69) for patients with watchful waiting before allogeneic HSCT (97 [72%] of 135 patients) and 32% (16–48) after anti-leukaemic treatment (38 [28%] patients; log-rank p=0·023 figure 3A). In the remission induction

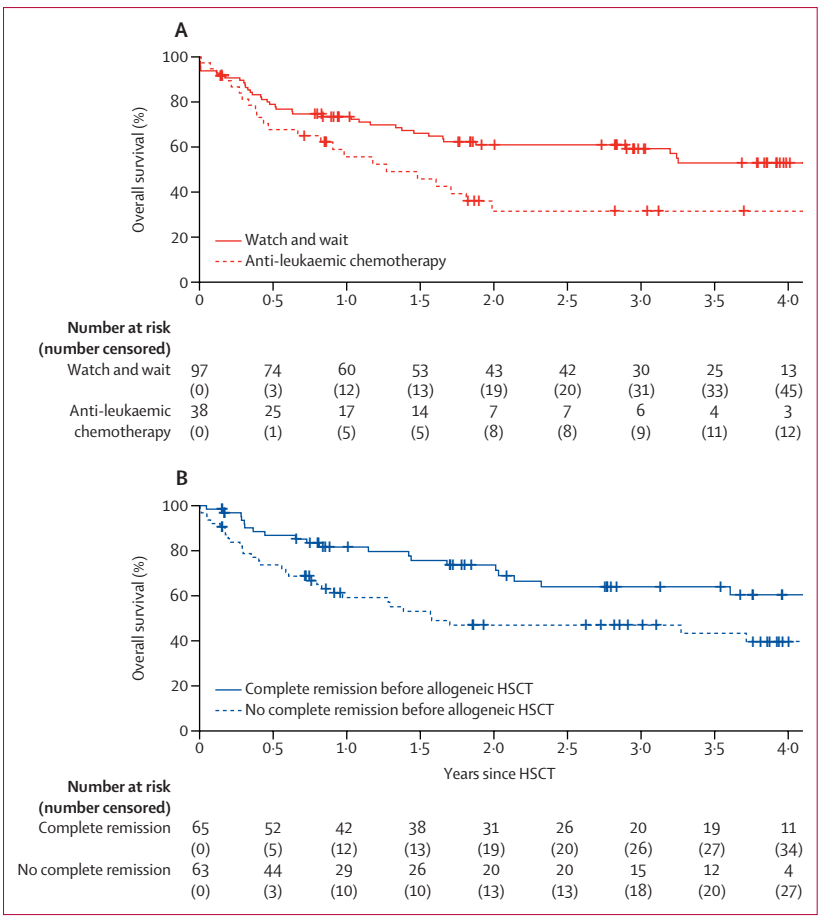

Figure 3: **Overall survival after transplantation by measures for the disease control group and by response to salvage chemotherapy**
HSCT=haematopoietic stem-cell transplantation.

group, 3-year overall survival after allogeneic HSCT was 64% (95% CI 49–76) for patients with complete remission after salvage chemotherapy (65 [51%] of 128 patients) and 47% (33–59) for patients with refractory acute myeloid leukaemia (63 [49%] of 128 patients; log-rank p=0·0066; figure 3B). Sankey plots, event-free survival, and overall survival after allogeneic HSCT for the two study groups are shown in the appendix (pp 24–25).

Before allogeneic HSCT, patients in the disease control group spent a median of 27 days less in hospital than those in the remission induction group (p<0·0001), ie, the median time in hospital was 15 days (range 7–64) with disease control versus 42 days (27–121) with remission induction. Time in hospital after allogeneic HSCT was not different. By day 28 after transplantation, 75% of patients (95% CI 67–82) in the disease control group compared with 73% of patients (66–81) in the remission induction group (*Z* test, p=0·80) were outpatients.

Fewer patients with disease control compared with remission induction had non-haematological adverse events grade 3 or worse (30 [21%] of 140 patients *vs* 86 [61%] of 141 patients, χ^2 test p<0·0001; table 2). The most common non-haematological toxicities in both groups were infections (22 [16%] of 140 patients *vs* 78 [55%] of 141 patients, χ^2 test p<0·0001). The Haematopoietic Cell Transplantation-specific Comorbidity Index deteriorated between randomisation and allogeneic HSCT in 33 (24%) of 135 patients in the disease control group compared with 52 (40%) of 130 patients in the remission induction group (χ^2 test p=0·0086, appendix p 33). In the per-protocol population the cumulative incidences of acute graft-versus-host disease grades 2–4 by day 120 after allogeneic HSCT were 22% (95% CI 15–29) in the disease control group and 21% (14–28) in the remission induction group (appendix p 17). Cumulative incidences of moderate or severe graft-versus-host disease at 1 year after allogeneic HSCT were 18% (95% CI 11–24) and 26% (18–34), respectively (appendix p 17). Graft-versus-host disease-free survival after HSCT did not differ statistically between patients randomly assigned to disease control versus remission induction (appendix pp 22, 37).

Between randomisation and the start of conditioning, two patients died from progressive acute myeloid leukaemia and zero from treatment-related complications in the disease control group, and two patients died from progressive acute myeloid leukaemia and two from treatment-related complications in the remission induction group (table 2). All-cause mortality was not statistically different between the two study groups at early timepoints from randomisation (4 weeks, 8 weeks, and 24 weeks; appendix pp 16–17). Infectious complications accounted for most deaths early in the course after allogeneic HSCT (appendix p 19). In total, 8 (6%) of 135 patients (95% CI 4–12) died within 28 days in the disease control group compared with 6 (5%) of 128 patients (2–10) in the remission induction group (p=0·65; appendix p 19). In the remission induction group, day 28 mortality after allogeneic HSCT was lower among patients who proceeded to allogeneic HSCT in complete remission (1 [2%] of 65 patients, 95% CI 0–5) compared with those not in complete remission (5 [8%] of 63 patients, 1–14; *Z* test p=0·085). Causes of death in the first 2 months after allogeneic HSCT are listed for both study groups in the appendix (pp 18–19).

Discussion

For patients with relapsed or refractory acute myeloid leukaemia, allogeneic HSCT offers the best chances for sustained disease control and long-term survival. The procedure itself and potential complications afterwards, however, are challenging in many ways. Randomised controlled trials, which inform about bridging therapies before allogeneic HSCT, are lacking.

In the ASAP trial, the benefit of salvage chemotherapy to induce complete remission before allogeneic HSCT was questioned. This trial enrolled patients eligible for a transplantation with non-favourable-risk acute myeloid leukaemia not in complete remission after first induction

	Disease control (n=140)				Remission induction (n=141)				p value
	Grade 3	Grade 4	Grade 5	Grade 3–5	Grade 3	Grade 4	Grade 5	Grade 3–5	
Total	39; 26 (19%)	6; 5 (4%)	2; 2 (1%)	47; 30 (21%)	140; 78 (55%)	18; 16 (11%)	4; 4 (3%)	162; 86 (61%)	<0·0001
Infection	24; 20 (14%)	3; 3 (2%)	0	27; 22 (16%)	98; 72 (51%)	8; 8 (6%)	1; 1 (1%)	107; 78 (55%)	<0·0001
Metabolic disorder	6; 6 (4%)	0	0	6; 6 (4%)	10; 7 (5%)	3; 3 (2%)	0	13; 10 (7%)	0·45
Cardiac disorder	0	0	0	0 (0%)	9; 8 (6%)	3; 3 (2%)	0	12; 11 (8%)	0·0022
Bleeding	1; 1 (1%)	1; 1 (1%)	0	2; 2 (1%)	3; 3 (2%)	3; 2 (1%)	1; 1 (1%)	7; 6 (4%)	0·29
Gastrointestinal toxicity	1; 1 (1%)	0	0	1; 1 (1%)	7; 6 (4%)	0	0	7; 6 (4%)	0·13
Liver toxicity	1; 1 (1%)	0	0	1; 1 (1%)	6; 4 (3%)	0	0	6; 4 (3%)	0·37
Acute myeloid leukaemia progression	0	0	2; 2 (1%)	2; 2 (1%)	0	0	2; 2 (1%)	2; 2 (1%)	1·0
Allergic reaction	1; 1 (1%)	0	0	1; 1 (1%)	2; 2 (1%)	0	0	2; 2 (1%)	1·0
Kidney toxicity	1; 1 (1%)	0	0	1; 1 (1%)	1; 1 (1%)	1; 1 (1%)	0	2; 2 (1%)	1·0
Malignancies	0	1; 1 (1%)	0	1; 1 (1%)	1; 1 (1%)	0	0	1; 1 (1%)	1·0
Pain	2; 2 (1%)	0	0	2; 2 (1%)	0	0	0	0 (0%)	0·47
Rash or exanthem	0	0	0	0 (0%)	2; 2 (1%)	0	0	2; 2 (1%)	0·48
Thromboembolic events	2; 2 (1%)	0	0	2; 2 (1%)	0	0	0	0 (0%)	0·47
Neuropsychiatric disorder	0	0	0	0 (0%)	1; 1 (1%)	0	0	1; 1 (1%)	1·0
Vascular disorder	0	1; 1 (1%)	0	1; 1 (1%)	0	0	0	0 (0%)	1·0

Data are the number of adverse events; number of patients with this adverse event (%). Adverse events grades 1 and 2 were not collected. p values correspond to the comparison of rates of adverse events grades 3–5 in both groups by means of χ^2 tests.

Table 2: **Grade 3 or worse non-haematological adverse events**

or untreated first relapse acute myeloid leukaemia. Allogeneic transplantation was intended for all patients in both groups. As a key feature, this trial displayed the entire selection process for allogeneic HSCT. Results of the disease control group show that patients with active acute myeloid leukaemia before the start of conditioning can have good survival prospects. This observation was in line with evidence from several phase 2 studies and retrospective analyses of patients with high-risk acute myeloid leukaemia transplanted in aplasia after the first or second course of induction chemotherapy,[8,9] and patients with untreated relapsed or refractory disease.[11,13,14,19] On the basis of data from these trials, our assumptions for rates of allogeneic HSCT (83% and 70%) and of treatment success (68% and 55%) were considerably lower for the disease control group and remission induction group. The 95% CI for the observed difference in success rates ranged from a 12% higher rate of treatment success rate with disease control to a 6% lower rate compared with remission induction. The lower end of the CI at 6% was less than the pre-specified 5% non-inferiority margin for confirmatory testing and thus non-inferiority could not be stated. However, the 5% non-inferiority margin should be applied with caution with the higher treatment success rates of 83% versus 79% in ITT population compared with the 68% and 55% rates of treatment success for disease control versus remission induction, which were assumed for sample size calculations, respectively. In line with these high rates of treatment success, much higher transplantation rates of 96% versus 93% in the disease control group and remission induction group, respectively, were found compared with previous intention-to-transplant trials. However, the results do not suggest an advantage from salvage chemotherapy before allogeneic HSCT either. Patients who underwent salvage chemotherapy to induce complete remission before allogeneic HSCT gained no benefit in treatment success or overall survival. Post-hoc calculations show that the ASAP trial had 80% power with the given observation times and observed survival rates to detect differences in 1-year survival of 13% or more. Since the treatment framework of transplanting patients with acute myeloid leukaemia in complete remission is not based on evidence from randomised controlled trials, this trial thus provides important information.

Allogeneic HSCT with active disease is common practice for patients with myelodysplastic or myeloproliferative neoplasia.[20,21] In line with the extensive clinical experience coming from patients with myelodysplastic syndrome, who show reasonably good outcomes when transplanted with active disease, the results of the ASAP trial also show that patients with active acute myeloid leukaemia before the start of conditioning show good outcomes. This information is especially relevant for patients with the new diagnostic category MDS/AML and patients with acute myeloid leukaemia-defining genetic abnormalities and less than 20% marrow blasts according to ELN 2022.[17]

How can the good results after allogeneic HSCT for active acute myeloid leukaemia in the ASAP trial be aligned with data from retrospective studies, which showed poor outcomes associated with persistent measurable residual disease before allogeneic HSCT?[5,6]

Many patients with measurable residual disease-positive disease in these retrospective studies had aggressive acute myeloid leukaemia biology, advanced disease stages, or multi-drug resistant relapsed or refractory disease.[22–24] While measurable residual disease after intensive acute myeloid leukaemia therapy reflects tumour load, even more importantly, it informs about treatment resistance, which is closely related to adverse-risk acute myeloid leukaemia biology. Data from the ASAP trial showed that tumour load itself was not associated with poor outcomes when intensive conditioning regimens were applied. Yet, adverse acute myeloid leukaemia biology clearly conferred a poor prognosis after allogeneic HSCT, also in the ASAP trial.

To interpret detectable measurable residual disease as a marker for treatment resistance, is in line with data published in 2022 from a large cohort of patients with acute myeloid leukaemia diagnosed at ages 60 years and older who had allogeneic HSCT in their first complete remission.[25] This study from the Dana Farber Cancer Institute showed that measurable residual disease-positivity before allogeneic HSCT was a strong negative risk factor in univariable comparisons but lost its prognostic value after adjusting for acute myeloid leukaemia biology with multivariate regression modelling.

This study has several limitations. First, despite promising long-term outcomes, peri-transplantation mortality was high for patients with active acute myeloid leukaemia. Especially, the safety and efficacy of conditioning regimens for this group of patients has to be further improved. Notably, in the randomised Figaro trial, patients with measurable residual disease-positive complete remission before allogeneic HSCT did not benefit from sequential conditioning with FLAMSA–busulfan versus reduced intensity conditioning, probably related to intensive pre-treatment.[26] The result, however, stresses the need for randomised controlled comparisons of conditioning regimens for patients with well defined disease-stages. Second, patients with *FLT3*-ITD mutated acute myeloid leukaemia were underrepresented in the ASAP trial. FLT3-inhibitors are superior compared with chemotherapy for this subtype and might represent a more attractive bridge to allogeneic HSCT.[27] Since the approval of gilteritinib in Europe, FLT3-inhibitors are considered for all patients with relapsed or refractory acute myeloid leukaemia before allogeneic HSCT. Patients with other types of hyperproliferative acute myeloid leukaemia might also be underrepresented, especially because patients with white blood cell counts of more than 50×10^9 cells per L were not eligible. For those patients, it remains unclear if and for how long disease control measures can be maintained safely. Third, patients with CNS manifestations of acute myeloid leukaemia were not eligible. In general, patients with extramedullary manifestations of acute myeloid leukaemia can benefit from an immediate start of anti-leukaemic chemotherapy because of a greater risk of complications than for patients without extramedullary acute myeloid leukaemia. Watchful waiting before allogeneic HSCT might not be appropriate for this patient group. Fourth, new strategies to induce complete remission are promising.[28] It is possible that, for example, venetoclax-based salvage regimens show a more favourable risk–benefit profile for remission induction before allogeneic HSCT than classical salvage chemotherapy.[29–31] Still, superiority of remission induction before allogeneic HSCT with such regimens as compared with immediate allogeneic HSCT should be shown in controlled trials. Fifth, ASAP transplantation depended on the availability of a suitable allogeneic stem cell donor. Thus, the donor search should be initiated immediately after diagnosis of adverse risk acute myeloid leukaemia or observation of treatment resistance. Sixth, information on the ethnic background of patients and donors was not collected. Patients diagnosed with acute myeloid leukaemia in Germany are usually homogeneous with respect to ethnicity and more than 95% are White. Our findings can thus not be translated one to one to patients and donors with more diverse ethnic backgrounds. For ethnicities for whom less volunteers are registered in donor registries worldwide, an unrelated donor search often takes more time or is unsuccessful. Transplantation from haploidentical donors is an attractive option for those patients but was not investigated in this trial. Seventh, patient enrolment took longer than expected due to a variety of factors, among them a lower number of participating centres than expected, competing trials, and the reluctance of patients to be randomly assigned to remission induction encompassing a longer stay in hospital before allogeneic HSCT. This long recruitment period opened the possibility for patient selection and changing treatment frameworks, eg, the approval of gilteritinib. Eighth, it would be desirable to know, if salvage chemotherapy is dispensable, for distinct genetic acute myeloid leukaemia entities, beyond patients that carry *FLT3*–ITD–TKD mutations. Especially for patients with high-risk genetic subtypes of acute myeloid leukaemia, exploring the possibility of early response assessment and immediate allogeneic HSCT to prevent further treatment resistance would be an attractive option. Patient numbers in the ASAP trial were too small to make robust statements for small subgroups. Finally, implementing the possibility of haploidentical donor transplantation in successor trials would be important to extend the possibility of immediate transplantation to a larger number of patients.

At the same time, the lack of benefit by salvage chemotherapy before allogeneic HSCT together with the absence of evidence in favour of remission induction coming from other randomised controlled trials constitute a dilemma. It is justified to question, for example, if patients with untreated molecular relapse of acute myeloid leukaemia benefit from salvage

chemotherapy before allogeneic HSCT. Therefore, given the far-reaching consequences from the patient's perspective, but also from an economical perspective, more randomised controlled intention-to-transplant trials are needed to define the optimal treatment before allogeneic HSCT for patients with defined genetic subgroups of acute myeloid leukaemia.

In conclusion, non-inferiority of a disease-control strategy compared with remission induction before allogeneic HSCT could not be shown within pre-defined statistical boundaries. Also, superiority of remission induction over disease control before allogeneic HSCT was not observed. Given the lack of evidence from randomised controlled trials for remission before allogeneic HSCT, results of the ASAP trial suggest immediate allogeneic HSCT as an alternative option for patients with relapsed or refractory acute myeloid leukaemia eligible for a transplantation. If a stem cell donor is readily available, salvage chemotherapy can possibly be omitted and immediate allogeneic HSCT with an intensive conditioning regimen can be offered without compromising long-term leukaemia-free survival. This option offers a chance for patients to spend less time in hospital and to reduce the cumulative treatment burden. For patients with *FLT3*-mutated relapsed or refractory acute myeloid leukaemia, administration of regimens including FLT3-inhibitors before and after allogeneic HSCT should be considered.

Contributors

JSche, MSt, MB, GB, CSchm, SWK, CRö, WEB, HS, GE, and AHS contributed to the conception and design of the trial. AHS, CP, JMM, CRö, and FS provided administrative support. MSt, JMM, GB, E-MW-D, LPM, CSchm, SWK, WB, EJ, UP, SAK, JSchu, JN, MK, KS-E, MSc, FS, CRö, NA, BS, BH, CSchl, KS, FL, OK, JScha, CRe, MB, J-HM, GE, and JSche provided study materials or recruited patients. CP and JSche collected and assembled the data. CP, HB, and JSche had access to the raw data. HB contributed to the statistical analysis. HB, MSt, MB, GB, J-HM, E-MW-D, LPM, CSchm, CRö, JMM, and JSche contributed to the analysis and interpretation of the data. JSche, MSt, JMM, MB, GB, and J-HM contributed to writing the manuscript. All authors approved of the final manuscript and are accountable for all aspects of the work.

Declaration of interests

MSt has served as a consultant for Pfizer, MSD, Bristol-Myers Squibb (BMS), Incyte, Takeda, and Amgen; as a speaker for Pfizer, Medac, MSD, Jazz Pharmaceuticals, Amgen, Novartis, Gilead, Celgene, BMS, AbbVie, and Incyte; has received research funding from Pfizer; and has received travel support from Medac and Pfizer. JMM received research funding from Janssen, Jazz, Astellas, and Novartis; consulting fees from Janssen, Roche, Gilead, AbbVie, Jazz Pharmaceuticals, Pfizer, Astellas, Novartis, AstraZeneca, and Glycostem; honoraria from Novartis, Roche, Janssen, AbbVie, Pfizer, Sanofi, Astellas, and BeiGene; and travel support from BeiGene. GB has received honoraria from Jazz Pharmaceuticals, Gilead Sciences, Novartis, BMS, and Otsuka; has served as a consultant for Novartis and Gilead Sciences; has received research funding from Novartis; and has received travel support from Gilead Sciences and Jazz Pharmaceuticals. LPM has served as a consultant for Pfizer, Amgen, Gilead Sciences, and Novartis; has received research funding from Amgen; and has received travel support from Gilead Sciences. CSchm has received honoraria for lectures, speaker bureaus, manuscript writing, and educational events from Novartis, Jazz Pharmaceuticals, and Neovii. SWK has received honoraria from Kosmas and Eickeler; and travel support from AbbVie, Jazz Pharmaceuticals, and Alexion Pharmaceuticals. WB has received lecture fees from Medac and participated in advisory boards for Gilead, Novartis, Miltenyi, Janssen, and BMS. EJ has received honoraria for lectures from BMS, Jazz Pharmaceuticals, Kite (a Gilead company), and Amgen; payment for expert testimony from Pierre Fabre; and travel support from Medac. UP has received consulting fees from Novartis, AbbVie, BMS, Silence, Sobi, AstraZeneca, Geron, GSK, Gilead, Jazz Pharmaceuticals, Syros, Akeso, Pierre Fabre, Curis, Galapagos, and Servier; honoraria for lectures from Novartis, AbbVie, BMS, and Janssen; travel support from AbbVie, Janssen, and Jazz Pharmazeuticals; and has participated in data safety monitoring board and advisory board meetings for AbbVie, Novartis, Jazz Pharmaceuticals, Nanexa, BMS, and Blueprint. SAK has served as a consultant for Novartis and Pfizer. MK has received lecture fees from Servier; travel support from Janssen and Kite (a Gilead company); and has participated in data safety monitoring and advisory board meetings for Gilead. KS-E has participated in data safety monitoring and advisory board meetings for Kite (a Gilead company). BH has received travel support from Jazz Pharmaceuticals, Janssen, and Kite (a Gilead company). FS has received lecture fees from Jazz Pharmaceuticals, Medac, and Pfizer; participated in advisory boards for Glycostem; and has received travel support from Servier, Medac, and Janssen. NA has received consulting fees from Amgen, Pfizer, AstraZeneca, and MSD and travel support from Amgen and Pfizer. BS has received travel support from AbbVie and Jazz Pharmaceuticals. CSchl has received honoraria from Novartis, AbbVie, Pfizer, AstraZeneca, and Jazz Pharmaceuticals; has served as a consultant for AbbVie, Jazz Pharmaceuticals, Pfizer, Novartis, Takeda, Roche, AstraZeneca, BMS and Celgene, Astellas Pharma, and Laboratories Delbert; has received research funding from AngioBiomed, Boehringer Ingelheim, and Jazz Pharmaceuticals; and has received travel support from Celgene, PharmaMar, Pfizer, AbbVie, and BMS and Celgene. KS received research funding from Active Biotech; has received honoraria from Novartis, BMS and Celgene, and GSK; has served as a consultant for Novartis, BMS and Celgene, and GSK; and has received travel support from Sobi. FL has received consulting fees, lecture fees, research support, and payments for expert testimony from Novartis and has participated in data safety monitoring board and advisory board meetings for Novartis, Pfizer, Incyte, and Biosciences. OK has received honoraria from Jazz Pharmaceuticals, Stemline Therapeutics, Janssen Oncology, and Pfizer and has received travel support from Jazz Pharmaceuticals and AstraZeneca. JScha has received travel support from Gilead and Jazz Pharmaceuticals. CRe has received travel support from Medac and Gilead Sciences. WEB holds stock and other ownership interests in Philogen; has received honoraria from Philogen; has served as a consultant for Philogen; has received research funding from Philogen; holds international patent rights for vascular targeting of tissue factor and siRNA targeting—so far without any return of money and is co-owner and CEO of two biotech start-ups, Anturec and Elvesca; has given expert testimony for Philogen; and has received travel and accommodation expenses from Philogen. HS holds stock and other ownership interests in Intellia Therapeutics, Biontech, and Arvin and Kymera; has received honoraria from Novartis, Robert-Bosch-Gesellschaft für Medizinische Forschung mbH, and Gilead Sciences; has served as a consultant for Gilead Sciences, IKP Stuttgart, and AbbVie; holds patent and other intellectual properties on Samhd1 modulation for treating resistance to cancer therapy, on oncogene redirection, on companion diagnostics for leukaemia treatment, and on markers for responsiveness to an inhibitor of *FLT3*. GE owns Cellex Cell Professionals. MB received honoraria from Jazz Pharmaceuticals, Alexion Pharmaceuticals, ActiTrexx, and MSD Oncology and has received travel support from Jazz Pharmaceuticals and MSD. J-HM has received consulting fees from Jazz Pharmaceuticals and Novartis; payments for lectures from BMS, Pfizer, Celgene, Novartis, Jazz Pharmaceuticals, BeiGene, and Daiichi Sankyo; and participated in data safety monitoring board or advisory board meetings for Pfizer and Daiichi Sankyo. JSche participated in advisory boards for AbbVie, AstraZeneca, BeiGene, BMS, Sanofi, Medac, MSD, and Janssen and received lecture fees from Astellas, AstraZeneca, BeiGene, BMS, Novartis, Eurocept, and Janssen. All other authors declare no competing interests.

Data sharing

The study protocol and associated documents (ie, informed consent forms, statistical analysis plan, safety manual, risk management plan, and monitoring plan) are available on request to the corresponding author. Individual participant data that underlie the results reported in

this Article, can be accessed from academic researchers after de-identification beginning 18 months and ending 48 months following Article publication. Interested researchers have to specify the aims and the proposed methods in a written research proposal to request data access. This proposal will be subject to an independent review. Data access will be granted, if the proposal receives a positive evaluation from the independent review committee and a data transfer agreement has been signed to comply with the EU directive on data protection.

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