Amsacrine combined with etoposide and methylprednisolone is a feasible and safe component in first-line intensified treatment of pediatric patients with high-risk acute lymphoblastic leukemia in CoALL-08-09 trial

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Abstract

Background The prognosis of children with acute lymphoblastic leukemia (ALL) has improved considerably over the past decades. However, to achieve cure in patients with refractory disease or relapse new treatment options are mandatory. Methods In the multicenter-trial CoALL-08-09, an additional treatment element consisting of the rarely used chemotherapeutic agent amsacrine combined with etoposide and methylprednisolone (AEP) (amsacrine 2 x 100 mg/m2, etoposide 2 x 500 mg/m2 and methylprednisolone 4 x 1000 mg/m2) was implemented into the first-line treatment of pediatric patients with a poor treatment response at the end of induction (EOI) measured by minimal residual disease (MRD). These patients were stratified into a high-risk intensified arm (HR-I) including an AEP element at the end of consolidation. Patients with induction failure (IF), i.e. lack of cytomorphological remission EOI, were eligible for hematopoietic stem cell transplantation (HSCT) after remission had been reached later on. These patients received AEP as a part of their MRD-guided bridging-to-transplant treatment. Results A significant improvement in probality of overall survival (pOS) for the CoALL-08-09 HR-I patients was noted compared to MRD-matched patients from the preceding CoALL-07-03 trial in the absence of severe or persistent treatment-related toxicities. Relapse rate and probability of event-free survival (pEFS) did not differ significantly between trials. In patients with IF a stable or improved MRD response after AEP was observed without severe or persistent treatment-related toxicities. Conclusion In conclusion, AEP is well-tolerated as a component of the HR treatment and useful in bridging-to-transplant settings.

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Abbreviations

AEP	amsacrine, etoposide, methylprednisolone
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
CNS	central nervous system
CoALL	cooperative study group for childhood acute lymphoblastic leukemia
CPM	cyclophosphamide
CTCAE	common terminology criteria for adverse events

AEP	amsacrine, etoposide, methylprednisolone
EOI	end of induction
IGH	immunoglobulin heavy chain
HR	high-risk
HR-I	high-risk intensified
HR-IF	high-risk induction failure
HSCT	hematopoietic stem cell transplantation
IF	induction failure
LR	low-risk
MRD	minimal residual disease
MTX	methotrexate
n.q.	non quantifiable
pOS	probability of overall survival
pEFS	probability of event-free survival
PEG-ASP	pegylated asparaginase
SAE	severe adverse event
SE	standard error
TCR	T cell receptor

Background

The prognosis of children with acute lymphoblastic leukemia (ALL) has improved considerably over the past decades. However, to achieve cure in patients with refractory disease or relapse new treatment options are mandatory.

Methods

In the multicenter-trial CoALL08-09, an additional treatment element consisting of the rarely used chemotherapeutic agent amsacrine combined with etoposide and methylprednisolone (AEP) (amsacrine 2 x 100 mg/m^2, etoposide 2 x 500 mg/m^2 and methylprednisolone 4 x 1000 mg/m^2) was implemented into the first-line treatment of pediatric patients with a poor treatment response at the end of induction (EOI) measured by minimal residual disease (MRD). These patients were stratified into a high-risk intensified arm (HR-I) including an AEP element at the end of consolidation. Patients with induction failure (IF), i.e. lack of cytomorphological remission EOI, were eligible for hematopoietic stem cell transplantation (HSCT) after remission had been reached later on. These patients received AEP as a part of their MRD-guided bridging-to-transplant treatment.

Results

A significant improvement in probability of overall survival (pOS) for the CoALL-08-09 HR-I patients was noted compared to MRD-matched patients from the preceding CoALL-07-03 trial in the absence of severe or persistent treatment-related toxicities. Relapse rate and probability of event-free survival (pEFS) did not differ significantly between trials. In patients with IF a stable or improved MRD response after AEP was observed without severe or persistent treatment-related toxicities.

Conclusion

In conclusion, AEP is well-tolerated as a component of the HR treatment and useful in bridging-to-transplant settings.

Introduction

Over the past 50 years the prognosis for children with ALL has improved markedly , but still refractory disease or relapse occurs in about 10 – 15 % of all patients.

Dose escalation of already used chemotherapeutic agents has been shown to be associated with a severe increase in short- and long-term toxicities and treatment-related mortality which abrogates the potential benefit for these patients . Upon initiation of the clinical trial CoALL08-09 in 2010, immunotherapy had not been approved precluding its integration into first-line protocols . For treatment intensification, we considered agents with proven biologic activity in refractory or multiply relapsed disease settings among which we identified the acridine derivative amsacrine (4'-(9-acridinylamino)-3-methoxyphenyl) methansulfon) . Amsacrine demonstrated promising efficacy in mostly adult patients with refractory acute myeloid leukemia (AML) when combined with etoposide or cytarabine. In addition, amsacrine in combination with etoposide and high-dose methylprednisolone was used as salvage therapy for relapsed and refractory ALL with moderate treatment-related morbidities Based on these results we introduced amsacrine, etoposide and high-dose methylprednisolone as a new add-on treatment element for primary high-risk ALL.

Patients presenting with a significant MRD load EOI or induction failure were eligible for the HR-I stratification and received a single AEP-block at the end of CoALL08-09 consolidation or as an individualized, MRD-guided off-protocol treatment subsequent to modified HR1 blocks (BFM-ALL 2000) to bridge to HSCT .

The anticipated number of patients in the HR-I group was too small to conduct a randomized evaluation of AEP compared to standard HR treatment. Hence, to determine the efficacy of the add-on AEP treatment element we performed a comparative analysis of a historical group of 42 HR patients from a previous trial (CoALL07-03) exhibiting a similar MRD level at EOI. These patients received the HR standard therapy without the AEP block.

To our knowledge, there has been no published clinical trial evaluating amsacrine as a component of first-line treatment of ALL at childhood. The primary objective of the trial CoALL-08-09 was to examine whether the introduction of potent second-line agents could reduce the risk of relapse in patients with HR-ALL without increasing treatment-related morbidity and mortality. The comparative non-randomized assessment of AEP in poor responding HR patients has been included as a post hoc study question.

Methods

Patients

In the multicenter clinical trial CoALL08-09 accrual was open from 1 October 2010 to 31 December 2019. A total of 745 patients aged >1 and < 18 years were enrolled in 8 cooperating trial centers in Germany. The study was approved by the ethics committee of the city of Hamburg and the institutional review boards of every individual trial center. Written informed consent was obtained from patients' parents or guardians in each case. The trial was registered at the ClinicalTrials.gov data base: GPOH-COALL 08-09 EU-21076 /NCT 0122 8331.

Stratification

All patients were stratified at diagnosis according to conventional risk criteria, allocating patients aged > 10 years, T or pro-B cell-immunophenotype (CD10 negative) or with a white blood cell count > 25/nl to the HR arm and all others to the low-risk (LR) arm. A second stratification was applied at EOI which included the state of cytomorphological remission and the results of in vivo treatment response (MRD) as well as the molecular and cytogenetic result. Patients with a *KMT2A* -rearrangement or a hypodiploid karyotype were additionally stratified to the HR arm. Within the LR and HR arm, patients were allocated to receive either a treatment reduction, standard treatment or treatment intensification based on their MRD result. All HR patients with a persisting high MRD-level at EOI (B-lineage-ALL: MRD [?] 10^{-3} at day 29, T-lineage-ALL: MRD [?] 10^{-3} at day 29 and day 43) were stratified to the HR-I treatment arm.

Patients presenting with a persistence of leukemic blasts [?] 5 % upon microscopic cytomorphological evaluation of the bone marrow with a corresponding MRD result at EOI were classified as induction treatment failure.

Treatment

Details of treatment for HR-I patients are summarized in figure 1. There were no major modifications in the treatment backbone compared to the preceding trial CoALL07-03 except a randomized comparison between high dose cytarabine and clofarabine both combined with asparaginase as the first consolidation block and the use of pegylated asparaginase (PEG-ASP) from the first dose onwards in CoALL08-09 whereas in the CoALL-07-03 native coli-asparaginase was scheduled for the first two asparaginase doses followed by PEG-ASP for the subsequent doses . For patients stratified into the HR-I treatment arm the AEP block was added to the treatment protocol at the end of the consolidation phase. Besides, in the central nervous system (CNS) phase an additional dose of daunorubicin, vincristine and PEG-ASP along with a seven-day course of dexamethasone was scheduled.

Patients that failed to achieve remission EOI were assigned to an MRD-guided treatment according to protocol which included (for details see supplemental table S1) . In case of MRD negativity after the first CoALL-HR1 block, patients resumed on-protocol therapy (HR-I arm) after the second CoALL-HR1 block. All patients with IF and MRD positivity after the first CoALL-HR1 block were eligible for an allogenic HSCT and received an AEP block after the second CoALL-HR1 block.

Analysis of minimal residual disease

Real-time quantitative polymerase chain reaction studies for MRD analysis were performed with immunoglobulin heavy chain (IGH) and T cell receptor (TCR) gene rearrangements as targets and interpreted according to the guidelines developed within the European Study Group for MRD detection in ALL . Ideally, two targets were used per patient, one with a quantitative range of 1 x 10^{-4} (0.01 %) and the second with a quantitative range of at least 5 x 10^{-4}(0.05 %). A sample was evaluated as MRD negative, if no positive signal was detected in any of three patient deoxyribonucleic acid replicate samples (500 ng genomic DNA per sample) for a specific target with a quantitative range of 0.01 %. In two cases, MRD was determined by multiparametric flow cytometry according to EURO-Flow MRD guidelines since the IGH- or TCR- MRD marker could not be established. In patients with failure of remission induction the MRD response was measured by determination of MRD before and after the first and second CoALL-HR1 block as well as prior and subsequent to the application of AEP.

Statistical analysis

The pEFS and pOS were estimated by using the Kaplan-Meier method . Comparison between the HR-I treatment (CoALL08-09) group vs. the historical standard HR-treatment (CoALL07-03) group was performed by using the log-rank test. pEFS was defined as the time from diagnosis to first event including relapse, death by any cause in remission, second malignancy or censoring at last follow-up. pOS was defined as the time from diagnosis to death by any cause or censoring at last follow-up.

The status of patients was monitored annually on protocol-specific forms reviewed by the trial data center before data entry. A recent update of the database (September 2021) was used for this analysis.

Toxicity reporting

Local trial centers conducted mandatory documentation of toxicities for each treatment element based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, modified by the German Society of Pediatric Oncology and Hematology on a patient-specific therapy flowsheet. In addition, treatment-related toxicities were documented in medical records. Severe adverse events (SAE) were reported instantaneously. Treatment-related toxicities were assigned to a specific treatment element, if they occurred during the application of chemotherapy or before the next treatment element had started.

As an additional surrogate marker for toxicity related to AEP treatment we calculated the duration from the start of AEP until the beginning of the subsequent therapy element.

Results

Patient characteristics

Of 745 patients included in CoALL08-09 89 patients (11.9 %) were allocated to the HR-I treatment arm according to MRD levels at EOI (figure 2). Twelve patients from the HR-I group did not receive AEP (six patients underwent SCT without prior AEP bridging treatment, three patients died before receiving AEP due to a treatment-related morbidity and three patients received other therapy modifications upon physicians' individual decision).

Fortytwo patients (5.6 %) were classified as failure of remission induction by morphology and confirmed by MRD analysis. Twenty of those did not receive AEP, because SCT was performed prior to AEP (nine patients), treatment-related mortality before AEP (two patients), allergic reaction to amsacrine (one patient) or other therapy modifications according to physicians' decision (eight patients). One patient had to be excluded from the response analysis in the AEP cohort because of lacking MRD data (figure 2).

The remaining 77 patients in the HR-I group and 22 patients prior to SCT received AEP and were therefore eligible and evaluable for this analysis.

There were 42 high-risk patients from the predecessor trial CoALL07-03 (4.9 % of all patients) with MRD EOI in a comparable range as the HR-I patients, i.e. B-lineage ALL: MRD [?] 10^{-3} at day 29 and T-lineage-ALL: MRD [?] 10^{-3} at day 29 and day 43. This patient cohort did not receive AEP as part of their consolidation treatment (figure 1) and was used for comparative analysis. The reason for the small proportion of patients with an MRD result in CoALL07-03 is the fact that MRD analysis was not used by default in the first three years of this trial. Due to substantial heterogeneity in treatment approaches we did not perform a comparative analysis of ALL patients with IF including historical control cohorts.

There was an equal distribution of sex and age in the different patient groups. With regard to the molecular genetic features we noted fewer*ETV6/RUNX1* $^{+}$ translocations among patients in the CoALL08-09 cohort without reaching statistical significance (table 1).

Outcome of HR-I patients in CoALL08-09 versus CoALL07-03

The 5-year pEFS of the whole cohort of HR-I patients in CoALL08-09 was 70.4 % with an overall survival of 86.2 % (intention-to-treat analysis, supplemental figures S1 and S2). The 5-year pEFS of the 77 HR-I AEP-treated patients was 72.9 % (SE 6.0) compared to 66.4 % (SE 7.3) pEFS under standard treatment in the HR-matched CoALL07-03 cohort (figure 3). This trend toward an improved event-free survival upon HR-I treatment reached significance in the comparative analysis of the overall survival of HR-I AEP treated patients (pOS 92.3 % (SE 3.4)) in CoALL08-09 vs. patients under standard HR-treatment (pOS 73.7 % (SE 6.8)) (p= 0.0038) in CoALL07-03 (figure 4). In a subgroup analysis according to immunophenotype patients with T-ALL showed a significantly improved event-free as well as overall outcome after HR-I AEP treatment in CoALL08- 09 (pEFS 85.1 % and pOS 92.3 %) compared to standard HR-treatment in CoALL07-03 (pEFS 54.5 % and pOS 63.6 %). In line with the outcome analyses of the overall HR-I and HR-standard cohorts the overall survival of patients with pB-ALL was superior in HR-I AEP-treated patients (CoALL08-09) compared with patients in the CoALL07-03 HR-standard arm (pOS 92.2 % vs. 77.3 %), whereas the difference in pEFS did not reach significance between HR-I AEP and HR-standard treated patients (supplemental figures S3-S6).

MRD response to AEP

To evaluate the efficacy of AEP treatment in the context of induction failure we monitored MRD in 21 patients presenting a failure of remission EOI prior and after AEP. In eight patients (31 %) a profound MRD reduction of at least half a log-fold was observed. It should be emphasized here that 5 of these 8 patients had a T-ALL immunophenotype. The remaining 13 patients (including 7 patients with a T-ALL) did not discernibly respond to AEP treatment at the molecular level, with no patient showing a serious increase in disease burden (table 2).

In patients within the HR-I arm MRD assessment was performed after the consolidation phase at the start of delayed intensification. In 44 of the 77 HR-I patients that had received AEP MRD results were available. Of

these 44 patients 38 (86%) had no measurable MRD, 2 patients had discernible but non-quantifiable (n.q.) MRD levels and only 4 patients still had quantifiable MRD burden. Fifteen of the 77 patients (19%) in the HR-I cohort who had received AEP suffered from relapsing disease. Interestingly, only 2 of those relapse-fated 15 patients showed a positive MRD at the start of delayed intensification, i.e. after AEP, whereas 7 of them showed negative results indicative of a declining predictive power of MRD negativity over time of treatment. In 6 patients who later on relapsed the MRD measurement was not available.

Assessment of AEP toxicity

Detailed toxicity data on AEP treatment were available from 94 patients (72/77 HR-I and from all 22 IF patients). Beside myelosuppression, infections accounted for the largest fraction among documented adverse complications (table 3). In the pooled analysis there were two reports of SAE caused by septicemia with Escherichia coli in the HR-I group and a perianal abscess formation among induction failure patients. Yet, no AEP-related death occurred. In thirty-four patients no toxicity was reported after AEP except an anticipated myelosuppression. The median time interval between the start of the AEP block and the subsequent CNS phase in late consolidation was 33 days (range: 19 to 69 days) which is comparable to other intensive chemotherapy courses .

Discussion

In the past decades treatment of ALL at childhood became more and more successful reflected by survival rates achieving greater than 90 % in high-resource developed countries . To further improve outcome in the rather small patient group with poor treatment response and a high risk of relapse, one aim of CoALL-08-09 trial was to find a new therapeutic option by adding a second line or salvage therapy element. As such, we implemented amsacrine into the frontline treatment of ALL and examined the efficacy and toxicity profile in combination with methylprednisolone and etoposide in late consolidation of patients with high EOI MRD ([?]10^{-3}).

In comparison to an MRD-matched historical control group of ALL patients recruited in trial CoALL-07-03, AEP treatment increased overall survival without impact on pEFS in HR-I patients under the CoALL-08-09 protocol. Time to relapse of matched patients did not differ between CoALL-07-03 and CoALL-08-09 cohorts but HSCT-related mortality was lower in the successor CoALL-08-09 trial likely accounting for the improvement of OS . A refined HSCT procedure including more precise donor selection, improved graft-versus-host disease prophylaxis and a more efficacious antifungal therapy might have contributed to this effect . In a T-ALL subgroup with high MRD burden AEP could have exerted an immediate effect on the risk of relapse by more efficacious eradication of residual leukemic clones as suggested by an improved pEFS. However, T-ALL subgroups in both trials are too small to draw firm conclusions.

In general, persistence of MRD throughout chemotherapy is associated with a poor prognosis, whereas early MRD negativity improves outcome significantly . The impact of MRD response to a single treatment element in consolidation treatment appears to be disputable. Yet, the level of MRD load prior to stem cell transplantation is a strong predictor of relapse . In the chemoresistant patient population with IF and a persistent MRD load the AEP block as part of a bridging-to-transplant procedure was shown to lower the MRD burden in a large proportion of patients without severe toxicity. Also in patients treated in the HR-I arm the side effects reported after the AEP block were rather moderate. Moreover, the average duration until the next therapeutic element as a surrogate parameter for myelosuppression was similar to other intensive therapy elements. By contrast, many study groups made the observation that very intensive chemotherapy was associated with an unusually high rate of side effects and increased treatment-related mortality .

The advances in immunotherapies offer alternative, potentially better treatment options for patients with refractory or relapsed leukemia compared to second-line chemotherapeutic agents such as amsacrine. CD19- and CD22-directed therapeutic antibodies have been licensed for several years. For instance, blinatumomab, a CD3/CD19-directed bispecific T cell engager, has been successfully used as a bridging-to-transplant approach leading to MRD-negativity in a substantial proportion of patients. Therapeutic antibodies exhibit a distinct toxicity profile mostly associated with a cytokine release syndrome or neurological side effects which could

preclude their application in some patients . In those patients and under conditions of very limited resources AEP-based intensification or bridging treatment could be a viable alternative to control MRD in HR-ALL patients, particularly in patients without CD19 surface expression on B-lymphoblasts that are not eligible for anti-CD19 directed therapies .

In conclusion, AEP is a well-tolerated and effective treatment element that can be applied as a part of the HR therapy or as an option in the process of bridging to HSCT in patients with ALL.

Conflict of interest statement

All authors declare no competing interests.

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Finally, we thank all the clinicians as well as diagnostics and research personnel who were actively involved in this clinical trial.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Legend list

Figure 1:

Treatment overview for HR standard therapy in CoALL07- 03 and for HR-intensified therapy in CoALL08-09:

CoALL07- 03 high- risk- standard:

I: Induction, vincristine (4x 1,5 mg/m^2) / daunorubicine (3x 36 mg/m^2) / methylprednisolone (60 mg/m^2/d for 28 days); C1a: cyclophosphamide (900 mg/m^2) / methotrexate (1 g/m^2) / E.coli asparaginase (45000 IE/m^2)/ methotrexate intrathecal (age-dependent dose); C1b: cyclophosphamide (900 mg/m^2) / methotrexate (1 g/m^2) / E.coli asparaginase (45000 IE/m^2) / 6-mercaptopurine (100 mg/m^2/d for 7 days) / methotrexate intrathecal (age-dependent dose); C2a: methotrexate (1 g/m^2) / teniposide (VM26) (165 mg/m^2) / cytarabine (300 mg/m^2) / 6-mercaptopurine (100 mg/m^2/d for 7 days) / methotrexate intrathecal (age-dependent dose); C2b: methotrexate (1 g/m^2) /teniposide (VM26) (165 mg/m^2) / cytarabine (300 mg/m^2) / 6-thioguanine (100 mg/m^2/d for 7 days) / methotrexate intrathecal (age-dependent dose); C3a: high- dose cytarabine (4x3 g/m^2) / pegylated asparaginase (2500 IE/m^2); CNS- phase: methotrexate intrathecal (3x age-dependent dose) / CNS- radiotherapy when indicated / 6-mercaptopurine (50 mg/m^2/d for 28 days); delayed intensification: vincristine (4x 1,5 mg/m^2) / doxorubicine (4x 30 mg/m^2) / pegylated asparaginase (2x 2500 IE/m^2) / cyclophosphamide (2x 900 mg/m^2) / cytarabine (8x 90 mg/m^2) / methotrexate intrathecal (3x age-dependent dose) / dexamethasone (2x 10 mg/m^2/d for 14 days) / 6-thioguanine (2x 100 mg/m^2/d for 7 days); maintenance: 6-mercaptopurine (daily per os, dose dependent on leukocyte count) / methotrexate (weekly per os, dose dependent on leukocyte count) / methotrexate intrathecal (3x age-dependent dose)

CoALL08- 09 high- risk- intensified:

Treatment backbone was identical except for the following differences:

- use of pegylated asparaginase (2500 IE/m^2) within block 1a, 1b and 3a.
- C3b: clofarabine (5x 40 mg/m^2), pegylated asparaginase (2500 IE/m^2), methotrexate intrathecal (age-dependent dose)
- AEP: amsacrine (2 x 100 mg/m^2), etoposide (2 x 500 mg/m^2) and methylprednisolone (4 x 1000 mg/m^2)

FIGURE 2:

Consort diagram for patients being eligible for AEP in CoALL08-09 trial

FIGURE 3:

5- year pEFS in CoALL08-09- HR-I patients undergoing AEP in comparison to HR ALL patients in CoALL07-03

FIGURE 4:

5-year pOS in CoALL08-09 HR-I patients undergoing AEP in comparison to HR patients from CoALL07-03

SUPPLEMENTAL FIGURE 1:

5- year pEFS in all HR-I patients from CoALL08-09 with or without AEP (intend to treat) in comparison to CoALL07-03

SUPPLEMENTAL FIGURE 2:

5- year pOS in all HR-I patients from CoALL08-09 with or without AEP (intend to treat) in comparison to CoALL07-03 without AEP

SUPPLEMENTAL FIGURE 3:

5- year-pEFS in B-precursor ALL HR-I patients treated according to CoALL08-09 with AEP in comparison to patients from CoALL07-03

SUPPLEMENTAL FIGURE 4:

5-year pOS in B-precursor ALL HR-I patients treated according to CoALL08-09 with AEP in comparison to patients from CoALL07-03

SUPPLEMENTAL FIGURE 5:

5-year pEFS in T- ALL HR-I patients treated according to CoALL08-09 with AEP in comparison to patients from CoALL07-03

SUPPLEMENTAL FIGURE 6:

5-year pOS in T-ALL HR-I patients treated according to CoALL08-09 with AEP in comparison to patients from CoALL07-03

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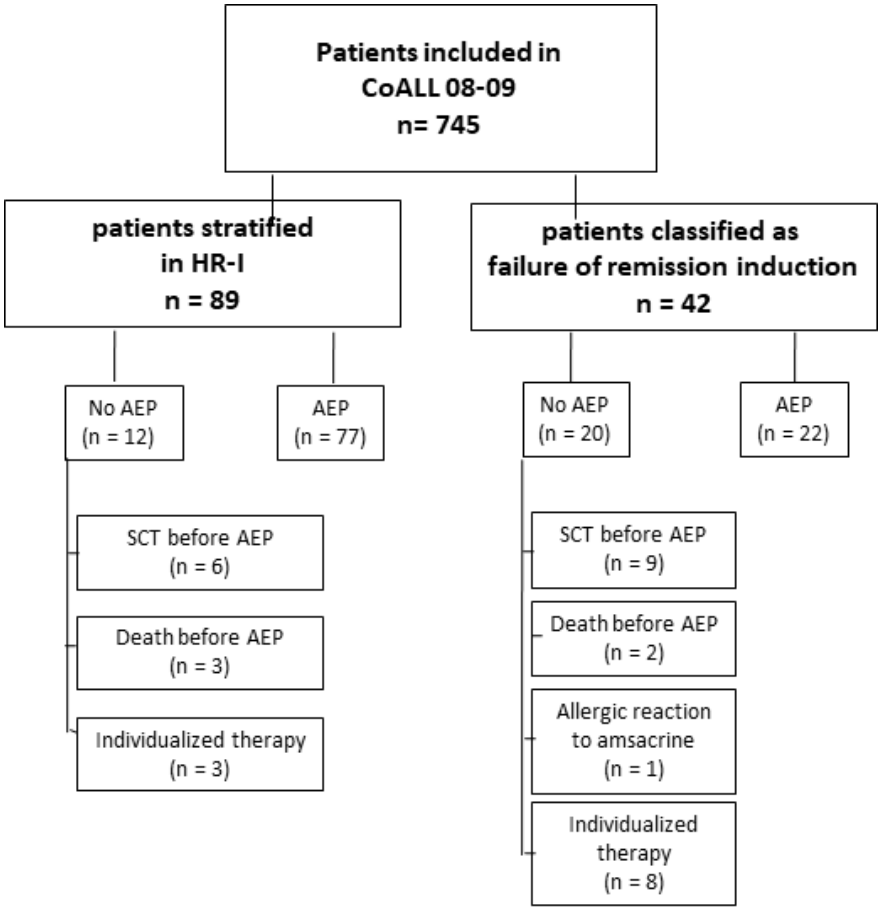

figure 2
Consort diagram for patients being eligible for AEP in CoALL 08-09 trial

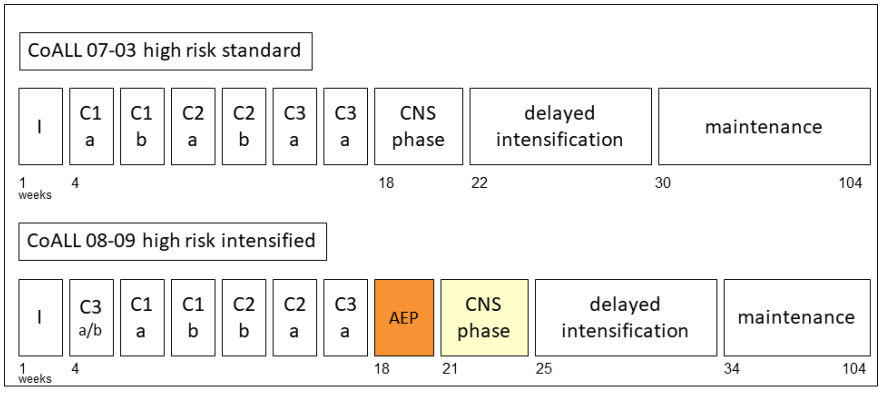

figure 1
Treatment overview for HR standard therapy in CoALL07- 03 and for HR-Intensified therapy in CoALL08-09