Acute myeloid leukemia

Successes and challenges in the treatment of pediatric acute myeloid leukemia: a retrospective analysis of the AML-BFM trials from 1987 to 2012

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Abstract

Overall survival (OS) of pediatric patients with acute myeloid leukemia (AML) increased in recent decades. However, it remained unknown whether advances in first-line treatment, supportive care, or second-line therapy mainly contributed to this improvement. Here, we retrospectively analyzed outcome and clinical data of 1940 pediatric AML patients (younger than 18 years of age), enrolled in the population-based AML-BFM trials between 1987 and 2012. While 5-year probability of OS (pOS) increased from 49 ± 3% (1987–1992) to 76 ± 4% (2010–2012; p < 0.0001), probability of event-free survival only improved from 41 ± 3% (1987–1992) to 50 ± 2% (1993–1998; p = 0.02) after introduction of high-dose cytarabine/mitoxantrone, but remained stable since then. Non-response and relapse rates stayed constant despite intensified first-line therapy (p = 0.08 and p = 0.17). Reduced fatal bleedings and leukostasis translated into fewer early deaths (8.1% vs. 2.2%; p = 0.001). Strikingly, pOS after non-response (13 ± 5% (1987–1992) vs. 43 ± 7% (2005–2010); p < 0.0001) or relapse (19 ± 4% vs. 45 ± 4%; p < 0.0001) improved. After 1999, more relapsed or refractory patients underwent hematopoietic stem cell transplantation (HSCT) with increased pOS after HSCT (29 ± 5% (1993–1998) vs. 50 ± 4% (2005–2010); p < 0.0001). Since efficacy of salvage therapy mainly contributed to better outcome in pediatric AML, our analysis indicates that a better allocation of patients, who cannot be cured with conventional chemotherapy, to an early “salvage-like” therapy is necessary.

Introduction

Prognosis of children with acute myeloid leukemia (AML) improved remarkably during the recent decades with current long-term survival rates of about 70% [1–5]. During this period, most international cooperative study groups have developed a treatment strategy that includes four to five courses of intensive myelosuppressive chemotherapy, mainly based on anthracyclines and cytarabine with or without hematopoietic stem cell transplantation (HSCT) [6]. This also applies to the AML-BFM trials, where several changes were introduced, concerning first-line treatment, supportive care, and second-line therapy.

The first-line treatment was intensified by introduction of courses with high-dose cytarabine or new anthracyclines or anthracycline formulations (Fig. 1a) [3, 7–10]. In the AML-BFM 87 trial, two cycles of late intensification with high-dose cytarabine (3 g/m²) and etoposide (HAE) were added after consolidation, while in the AML-BFM 93 trial, idarubicin during first induction therapy and an additional course with high-dose cytarabine (3 g/m²) and mitoxantrone...
(HAM) as second-induction cycle were introduced. In the AML-BFM 98 trial, a high-dose consolidation therapy (with comparable cumulative dosages of anthracyclines as before) was introduced with two short treatment cycles (cytarabine and idarubicine [AI], high-dose cytarabine (1 g/m²) and mitoxantrone (hAM)). In the AML-BFM 04 trial, liposomal daunorubicin, a potentially less cardiotoxic anthracycline formulation compared to idarubicin, was introduced together with an increase of the cumulative anthracycline dose (Fig. 1a) [2, 9, 11, 12].

In parallel, agents were sequentially integrated into international guidelines to advance supportive care. Antibacterial agents, such as antipseudomonal broad-spectrum β-lactam antibiotics or carbapenems, antifungal drugs especially caspofungin or liposomal amphotericin and antiviral medications, such as aciclovir or cidofovir were approved to face high infection-related mortality [13–17]. With rasburicase, a drug is approved by the US Food and Drug Administration since 2002 to overcome urate nephropathy as part of tumor lysis syndrome. Already since
AML-BFM 87 guidelines were made to face bleeding complications or leukostasis [18].

Lastly, trials were realized to assure a systematic and controlled approach after relapse or non-response. Although the first AML-BFM relapse study started in 1991 with low accrual rate, patients with relapse received diverse treatment regimen until 10/2001 [19]. The AML-BFM REZ 91 trial recommended a double induction of mitoxantrone and etoposid before proceeding to a 6-week consolidation and allogeneic or autologous HSCT. In study AML-BFM REZ 93, only one course of mitoxantrone and etoposid was given, followed by HAM and subsequent 6-week consolidation and either allogeneic or autologous HSCT. Both studies included a maintenance therapy [20]. Thereafter, patients were recruited to the first relapse study with appropriate patient accrual (AML-BFM REZ 97), which consisted of two blocks of reinduction with intermediate-dose cytarabine and liposomal daunorubicin, followed by allogeneic HSCT after consolidation [21]. Since 11/2001, a randomized phase III study (AML-2001/01) was opened by the International BFM (I-BFM) Study Group for pediatric patients with relapsed AML with FLAG (fludarabine, cytarabine, granulocyte-colony-stimulating factor) reinduction with or without liposomal daunorubicin, followed by a second FLAG block before proceeding to consolidation or direct to allogeneic transplantation or autologous transplantation in late relapse [22].

Although the importance of HSCT after relapse or non-response is well established, the role of HSCT in first complete remission (CR) continuously changed during the last decades [23, 24]. Several international protocols from the 1990s recommended allogeneic HSCT to all patients with matched sibling donor [25]. However, most of the recent trials use refined criteria based on risk stratification according to cytogenetic subgroups and response evaluation. Due to different definitions and indications, current transplantation rates vary from 11 to 29% [6, 25].

Thus, it remains largely unknown whether intensification of first-line treatment, better supportive care, or improved second-line therapy mainly contributed to the markedly increased overall survival (OS) in pediatric AML.

Here we present a retrospective analysis to delineate the possible causes for enhanced survival in pediatric AML, but also to reveal obstacles that may hamper further improvement. We analyzed response to first-line therapy, causes of death, survival after relapse or non-response, and the impact of HSCT in 1940 patients younger than 18 years of age with de novo AML that were enrolled in four consecutive AML-BFM trials (AML-BFM 87, AML-BFM 93, AML-BFM 98, and AML-BFM 04) between 1987 and 2012.

**Patients and methods**

**Patients**

Between 1/1987 and 12/2012, 1940 patients from 0 to 18 years of age with de novo AML in Germany, Austria (since 1993) and Switzerland were enrolled into the multicenter trials or registries of the AML-BFM studies. Any accompanying diseases that did not allow therapy according to the protocol or pre-treatment for >14 days with another intensive induction therapy resulted in exclusion of the patients from this study. We excluded patients with secondary leukemia, patients with Down syndrome myeloid leukemia or

**Fig. 1 Development of overall and event-free survival from 1987–2012.** a Protocol flow chart for pediatric patients with AML in AML-BFM trials from 87 until 2012. Consolidation: 6-week therapy consisting of seven different drugs: 6-thioguanine (60 mg/m² per day, days 1–4 orally); prednisone (40 mg/m² per day, days 1–28 orally); vincristine (1.5 mg/m² per day, days 1, 8, 15, 22); cytarabine (75 mg/m² per day, days 3–6, 10–13, 17–20, 24–27, 31–34, 38–41); doxorubicin (30 mg/m² per day (AML-BFM 87 and 93)) or idarubicin (7 mg/m² per day [AML-BFM 98], days 1, 8, 15, 22); intrathecal (age-dependent dose) cytarabine (days 1, 15, 29, 43); cyclophosphamide (500 mg/m² per day, days 29, 43). *CNS* irradiation was stopped in May 2009. Cumulative dosages of anthracycline (mg/m²) and cytarabine (mg/m²) in AML-BFM trials are shown as maximal dosage given in each study. Cumulative doses were calculated as equivalent doses to daunorubicin using a ratio of 1:5 for idarubicin and mitoxantrone. ADE cytarabine (100 mg/m²), daunorubicin (60 mg/m²), etoposide (150 mg/m²), AIE cytarabine (100 mg/m²), idarubicin (12 mg/m²), etoposide (150 mg/m²), HAM high-dose cytarabine (3 g/m²), mitoxantrone (10 mg/m²), AI cytarabine (500 mg/m²), idarubicin (7 mg/m²), HAM intermediate-dose cytarabine (1 g/m²), mitoxantrone (10 mg/m²), HAE high-dose cytarabine (3 g/m²), etoposide (125 mg/m²), ADxE cytarabine (100 mg/m²), liposomal daunorubicin (80 mg/m²), etoposide (150 mg/m²), 2-CDA 2-chloro-2-deoxyadenosine (6 mg/m²), CNS central nervous system. b Development of survival per 6-year periods. Data shown as probability of EFS and OS ± SE. Kaplan–Meier curves of EFS and OS of distinct subgroups were compared using the log-rank test, shown as p value. Development of survival per 6-year periods in patients with standard risk group [FAB M1/2 with Auer rods, FAB M4 with atypical eosinophils (M4Eo) and/or favorable cytogenetics, such as t(8;21) and/or AML1-ETO and inv (16) or t(16;16) and/or CBF/MYH11, if there was no persistence of BM blasts (≥5% on day 15, respectively), compared to all other patients (high-risk group). Data shown as probability of EFS and OS ± SE. Kaplan–Meier curves of EFS and OS of distinct subgroups were compared using the log-rank test, shown as p value. Standard risk: n = 88 (1987–1992); n = 174 (1993–1998); n = 151 (1999–2004); n = 148 (2005–2010); n = 39 (2011–2012). High-risk: n = 207 (1987–1992); n = 359 (1993–1998); n = 346 (1999–2004); n = 329 (2005–2010); n = 98 (2011–2012). d Overview of events (early death, death in CR, non-response, relapse, others) per 6-year periods. Data shown as probability of EFS ± SE and cumulative incidences of events. e Overview of survival and causes of deaths (caused by bleeding, infections or HSCT-related, disease-related deaths or others). Bleeding and infections have been evaluated in patients during initial disease and salvage treatment. Data shown as probability of OS ± SE and cumulative incidences of death. *Shorter interval for sufficient follow-up. n = 295 (1987–1992); n = 533 (1993–1998); n = 497 (1999–2004); n = 477 (2005–2010); n = 138 (2011–2012)
acute promyelocytic leukemia from analysis due to their unique biology and treatment. In addition, patients from Czech Republic were excluded to avoid bias due to their late inclusion in the AML-BFM studies and the expected learning curve.

National ethics committees and institutional review boards approved this study, and patients or guardians provided written informed consent. The study was performed in accordance with the Declaration of Helsinki.

**Treatment**

Patients from 1987 until February 2004 were treated and risk-stratified (Supplementary Material 1) according to the respective trial protocols with increasing intensity. Detailed protocols of AML-BFM 87, AML-BFM 93, and AML-BFM 98 are described elsewhere (see Fig. 1a and introduction) [12, 26, 27]. Cumulative doses were calculated as equivalent doses to daunorubicin using a ratio of 1:5 for idarubicin and mitoxantrone as previously described [28]. Between March 2004 and April 2010, patients were treated according to the AML-BFM 04 trial (ClinicalTrials.gov Identifier: NCT00111345) [2]. Allogeneic HSCT from matched sibling donors was limited to high-risk patients in first CR, and after an amendment in 2006, allogeneic HSCT was restricted to only high-risk patients with persistent disease after second induction (bone marrow blasts ≥5%) [29, 30]. The first recommendations regarding the conditioning regimen for allogeneic SCT in first CR, consisting of busulfan and cyclophosphamide, have been included in the AML-BFM 98 trial [29]. Since April 2010, patients were treated according to best arm of the AML-BFM 04 protocol. All patients received the liposomal formulation of daunorubicin during induction therapy, and all high-risk patients received 2-chloro-2-deoxyadenosine as intensification therapy during the cytarabine/idarubicin (AI) consolidation. Randomized cranial irradiation was stopped in May 2009 [30]. Patients with relapse received different treatment regimen until 10/2001. For detailed information, see introduction and results.

**Subgroup analysis**

To further analyze the impact of time or supportive care, all high-risk patients (n = 383) of the AML-BFM 98 and AML-BFM 04 trials, who have been treated homogeneously (AIE, HAM, AI, haM, HAE, maintenance, and no HSCT) have been included for a separate analysis of survival.

**Definitions**

The remission criteria were defined according to the Cancer and Leukemia Group B criteria at the end of intensification [31]. Probability of event-free survival (pEFS) was calculated as the time from diagnosis to the first event (relapse, death of any cause, failure to achieve remission, or secondary malignancy) or last follow-up. Failure to achieve remission was considered an event on day 0. Probability of OS (pOS) was defined as the time from the date of diagnosis to the date of death from any cause or last follow-up. Early death (ED): death within 42 days was considered early death. Patients were classified according to deaths caused by leukostasis or bleeding, infections, and others. Early relapse: all patients with relapse within 1 year after diagnosis. Medical reports of deceased patients were reviewed for evaluation of causes of deaths. More details on definitions including risk stratification are available in supplemental material.

**Statistical analyses**

Statistical analyses were performed with SAS version 9.03 (SAS Institute). The median follow-up was 10 years. The Kaplan–Meier method was applied to estimate probabilities of survival. EFS and OS curves of distinct subgroups were compared using the log-rank test. Cumulative incidence functions of relapse, relapse or non-response, and death in CR were constructed according to Kalbfleisch and Prentice. Competing events were all other events for pEFS: death before CR (early death) and secondary malignancy. Gray’s method was used to compare cumulative incidences. All cumulative incidence functions and survival estimates are calculated as 5-year time point. All p values are descriptive and explorative. The analysis was performed per 6-year periods (1987–1992 (n = 295); 1993–1998 (n = 533); 1999–2004 (n = 497); 2005–2010 (n = 477)). These periods reflect the recruitment times of the succeeding studies AML-BFM 87, 93, 98 and 2004. For a subset of analysis, we included patients diagnosed from 2011–2012 (n = 138), but only for investigations of initial disease as appropriate follow-up is required. For a subset of analysis, patients were grouped depending on age, always defined as age of diagnosis. Only patients with allogeneic HSCT have been included in the analyses of transplantation. For all analyses of risk group stratification, the following definition was used retrospectively: standard risk indicates FAB M1/2 with Auer rods, FAB M4 with atypical eosinophils (M4Eo) and/or favorable cytogenetics, such as t(8;21) and/or AML1-ETO and inv (16) or t(16;16) and/or CBFB/MYH11, if there was no persistence of bone marrow (BM) blasts (≥5%) on day 15. FLT3-ITD positivity was not considered. All others were classified as high-risk patients. The database lock for this analysis was set at 1 July 2016. Of the 1940 patients, 962 (576, 335) were alive at the time of data freeze and followed for at least 5 (10, 15) years.
Results

Development of overall and event-free survival from 1987 to 2012

The first-line treatment was intensified stepwise from 1987 to 2012 with increased cumulative doses of cytarabine (maximum 47 g/m² in AML-BFM 98) and anthracycline (maximum 510 mg/m² in AML-BFM 04; Fig. 1a). The 5-year pOS of 1940 patients registered in the AML-BFM studies showed a continuous, and significant improvement from 1987–1992 (49 ± 3%) to 2011–2012 (76 ± 4%; p < 0.0001; Fig. 1b). In contrast, the pEFS only increased significantly from 41 ± 3% (1987–1992) to 50 ± 2% (1993–1998; p = 0.02) after introduction of high-dose cytarabine/mitoxantrone, but remained stable since then (p = 0.21) (Fig. 1b). Thus, there is an increasing gap between pEFS and pOS (8%, (1987–1992) vs. 21%, (2011–2012)) (Fig. 1b). Subgroup analysis revealed that both, pEFS (p = 0.0029) and pOS (p < 0.0001), improved in patients with high-risk AML, while in patients with standard risk AML, only pOS increased (p = 0.0044) (Fig. 1c). Young patients (younger than 2 years of age) showed a benefit in pOS and patients older than 13 years of age showed a constant improvement of pEFS and pOS (Supplementary Figure 1A).
The impact of first-line treatment

Intensification of first-line therapy resulted in an insignificant reduction of the cumulative incidences of relapse (32 ± 3% vs. 25 ± 4%, p = 0.17) and non-response (16 ± 2% vs. 12 ± 3%, p = 0.08) from 1987 till 2012 (Fig. 1d and Supplementary Table 1). However, the rate of non-response significantly dropped between 1987–1992 and 1993–1998 (p = 0.025) (Supplementary Table 1). This drop was associated with an improved pEFS and coincided with the introduction of HAM (Fig. 1a). Moreover, there was a relevant change in causes of death during the first 6 weeks after initial diagnosis (early death). Whereas in earlier trials, deaths due to bleeding or leukostasis were most
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The increasing gap between pEFS and pOS after first-line therapy indicates that the survival after an event was improved. Therefore, we analyzed the impact of salvage therapy on the improved pOS (detailed information on protocols in Fig. 3a and introduction). Notably, the 5-year pOS of patients after relapse improved from 19 ± 4% (1987–1992) to 45 ± 4% (2005–2010; p < 0.0001), with the highest increase from 1999–2004 to 2005–2010 (28 ± 3% vs. 45 ± 4%; p = 0.0003) (Fig. 3d). The 5-year pEFS after relapse showed a comparable development from 19 ± 4% (1987–1992) to 40 ± 4% (2005–2010) (p < 0.0001) (Fig. 3b). The same significant increase in pEFS and pOS was observed in patients with non-response (Fig. 3c, e). The improvement coincided with the start of the relapsed AML 2001/01 I-BFM study. The changes in salvage therapy resulted in a considerable reduction of disease-related deaths in patients with relapse (64.1 ± 5.0 vs. 30.7 ± 3.8%; p < 0.0001) or non-response (52.1 ± 7.4 vs. 25.5 ± 6.5%; p = 0.0038) (Fig. 3d, e). Young patients had the highest benefit from improved salvage therapy (younger than 2 years of age: 14 ± 5% (1987–1992) vs. 56 ± 7%
(2005–2010); p < 0.0001 and 2–9 years of age: 13 ± 5% (1987–1992) vs. 45 ± 6% (2005–2010); p < 0.0001) (Supplementary Figure 1B).

Infectious-related deaths or bleeding-related deaths were significantly reduced in non-responders (20.8 ± 5.9% vs. 6.4 ± 3.6%; p = 0.042 or 10.4 ± 4.5% vs. 0.0 ± 0.0%; p = 0.024), while it was insignificantly reduced after relapse (infections: 9.3 ± 3.0% vs. 6.5 ± 2.0%; p = 0.39 or bleeding 2.1 ± 1.5% vs. 0.0 ± 0.0%; p = 0.07) (Fig. 3d, e).

The lower disease-related mortality after relapse or non-response was accompanied by a higher HSCT-related mortality (5.2 ± 2.3% vs. 16.9 ± 0.3%; p = 0.0075; Fig. 3d and 2.1 ± 2.1% vs. 21.3 ± 6.1%; p = 0.004; Fig. 3e), which can be explained by the higher number of patients that underwent HSCT (relapse: 22% (1987–1992) vs. 75% (2005–2010), p < 0.0001; non-response: 19% vs. 85%, p < 0.0001, Supplementary Table 3). Still, patients undergoing allogeneic HSCT after first relapse or non-response showed an improved survival, most notably after 1999 (29 ± 5% (1993–1998) vs. 50 ± 4% (2005–2010); p < 0.0001; Fig. 4a). The improvement over time was most prominent in patients with early relapse (0 ± 0% (1987–1992) vs. 47 ± 6% (2005–2010); p = 0.015), while the survival increased insignificantly in patients with late relapse (42 ± 13% (1987–1992) vs. 55 ± 7% (2005–2010); p = 0.41; Fig. 4b).

In contrast, patients of both groups showed a dismal survival without allogeneic HSCT that did not change over time. Patients with an initial standard cytogenetic risk profile showed a particular increase in pOS after HSCT after first relapse (34 ± 9% (1987–1998) vs. 60 ± 7% (1999–2010); p = 0.016; Fig. 4c), while for high-risk patients the pOS remained poor (35 ± 6% (1987–1998) vs. 42 ± 4% (1999–2010); p = 0.15; Fig. 4c).

Supportive care—a subgroup analysis

To analyze the role of supportive care for the improved survival independent of changes made to the treatment protocol, we performed a subgroup analysis of homogenously treated patients enrolled over a period of 12 years (n = 383). This was possible as one arm of all high-risk patients of the AML-BFM 98 and AML-BFM 04 trials was equal (Supplementary Figure 2A). We excluded patients with HSCT to avoid a bias through probably variable criteria for selection of HSCT and different procedures.

Patient characteristics were comparable between both groups (Supplementary Table 4). The survival analysis showed that pEFS, but also pOS did not change significantly (Supplementary Figure 2B). Similarly, despite of expanded supportive care recommendations (Supplementary Material 2) treatment-related mortality, including infectious deaths, did not change between both study populations (Supplementary Figure 2C).

Discussion

Long-term survival of children with AML has significantly improved within the recent decades [1–5]. In this retrospective analysis of 1940 pediatric patients treated within the AML-BFM protocols between 1987 and 2012, we deciphered the contribution of intensified first-line treatment, supportive care and salvage therapy to this success (summarized in Fig. 5). We showed that intensification of first-line therapy translated into an unsteady and insignificant improvement of pEFS over the past 25 years, which is mainly explained by a failure to significantly reduce the relapse or non-response rate. Only the major drug intensification in the AML-BFM 93 study (i.e., introduction of HAM) resulted in a significant increase of pEFS. Still, one must consider that improving the outcome was not only the aim of the AML-BFM trials. In the AML-BFM 98 and 04 trials, it could be shown in a randomized non-inferiority study that reduced cranial irradiation does not result in a survival disadvantage [30].

The better pOS despite a nearly constant rate of non-response and relapse since 1993 can be regarded as major advance of salvage therapy. The remarkably reduced disease-related mortality in patients with non-response and relapse assures nowadays a survival rate of 45% in these patients. This development, especially in young children, patients with early relapse or with an initial standard risk cytogenetic profile, is most probably due to a systematic treatment of patients after relapse or non-response and higher survival rates after transplantation. In particular, the better outcome after 1999 coincided with the introduction of the international relapse protocol and rising transplantation rates. Of note, survival after relapse already started to increase in patients enrolled in AML-Rez 97, but the patient accrual was still low. Interestingly, autologous SCT was only performed in a relevant percentage of patients in 1987–1992 (n = 21; 21.6% of all patients with first relapse).
In the following years, this procedure was only rarely used in a relapse setting \((n = 10; 6.3\% \text{ (1993–1998)}), n = 2; 1.2\% \text{ (1999–2004)}), n = 1; 0.6\% \text{ (2004–2010)}.\)

The impact of supportive care is more difficult to assess. An analysis with a subset of patients of this study, who have been treated with identical chemotherapy over 12 years, failed to show a significant change of pEFS and treatment-related mortality despite of more advanced recommendations. However, the small number of patients within this analysis and the retrospective design may limit this subgroup analysis. Different aspects of this study may illustrate the importance of advanced supportive care in pediatric AML. The reduced early death rate, especially due to bleeding or leukostasis, reflects improved supporting procedures and guidelines for cytoreductive therapy in case of hyperleukocytosis. Moreover, advances in supportive care may be the basis for the increase of patients with relapse proceeding to HSCT and for the improved survival after HSCT. This can be exemplified by a decreased infectious-related mortality especially in patients with non-response. A recent study reported a significantly reduced infectious-related mortality in AML-BFM 04 compared to historic data of the AML-BFM 93 study \([14, 32]\), especially in the first 42 days (early deaths group) or after achieving CR, which is in accordance with our study \([14, 33]\). Of note, in contrast to the previous study, we included treatment-related mortality during initial and relapse treatment. Yet, the significantly reduced infectious-related mortality in the aforementioned subgroups is counterbalanced by an increasing HSCT-related mortality. HSCT-related mortality is becoming increasingly important due to higher percentage of patients, being transplanted after extensive treatment in non-response or relapse, constituting a major challenge for the upcoming years. This means that critically sick patients are nowadays eligible for HSCT, which were previously excluded from this procedure. Nevertheless, the remarkably increasing survival rate of patients with HSCT underlines the progress that was achieved. However, prospective randomized studies in pediatric AML are difficult to perform and thereby the exact value for patients with HSCT in first CR is still unclear \([23–25]\). Since 2010 a prospective non-randomized, multinational, and on-site monitored BFM-HSCT trial for pediatric AML has been initiated aiming for therapy optimization. It includes patients with second CR or primary refractory disease, analyzing the role of matched sibling donors vs. matched unrelated donors, the effectivity of “FLAMSA” and in a subgroup of patients the relevance of haploidentical transplantation (EudraCT: 2007–004517–34, NCT00606723).

The trial could harmonize transplantation-related center effects and will better define the role of HSCT in the treatment of pediatric AML. Results of this trial will be separately reported.

In conclusion, we identified three main factors, which were responsible for improved outcome. First, treatment intensification from AML-BFM 87 to the AML-BFM 93 study resulted in a significant reduction of non-responders and relapses, which was not seen by treatment intensification in later studies. Second, the efficacy of second-line therapy including HSCT, which was consequently applied since 2001 according to an international study protocol, was most successful to improve outcome in pediatric AML during the last 25 years. Third, better supportive care contributed to reduce the early death rate and partly infectious-related deaths.

These findings of our retrospective analysis have important implications for the future. Further intensification of anthracycline- and cytarabine-based chemotherapy will most likely not result in a major reduction of relapse or non-response. The development of new classes of innovative drugs or immunotherapy in first-line therapy is required to enhance response and reduce the risk of relapse. Better stratification of patients based on their individual genetic risk and measurements of minimal residual disease would help to quickly allocate patients to a “salvage-like” therapy that cannot be cured with conventional first-line chemotherapy only. This should be ideally proven in a prospective study with long-term follow-up and monitoring of quality of life. And finally, further improvements in supportive care are urgently needed to keep pace with intensified toxicity, especially after HSCT.

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Compliance with ethical standards

Conflict of interest J.-P.B. has consulting or advisory roles for Amgen and Roche. T.K. has consulting or advisory roles for Loxo and Novartis. T.L. receives honoraria from Gilead, Merk Sharp & Dome, Astella, Basilea, and has consulting or advisory roles and participates in speakers’ bureaus, including travel accommodation and other expenses from Gilead, Merk Sharp & Dome, Astella. T.L. receives research funding from Gilead. D.R. has consulting or advisory roles for Roche, Celgene, Hexal, Pfizer, Novartis, Boehringer and receives research funding from Celgene. D.R. received travel, accommodation or other expenses from Jazz Pharmaceuticals and Griffols. The remaining authors declare that they have no conflict of interest.

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