Age-Related Risk Profile and Chemotherapy Dose Response in Acute Myeloid Leukemia: A Study by the German Acute Myeloid Leukemia Cooperative Group

Thomas Büchner, Wolfgang E. Berdel, Claudia Haferlach, Torsten Haferlach, Susanne Schnittger, Carsten Müller-Tidow, Jan Braess, Karsten Spiekermann, Joachim Kienast, Peter Staub, Andreas Grüneisen, Wolfgang Kern, Albrecht Reichle, Georg Maschmeyer, Carlo Aul, Eva Lengfelder, Maria-Cristina Sauerland, Achim Heinecke, Bernhard Wörmann, and Wolfgang Hiddemann

ABSTRACT

Purpose
The purpose of the study was to assess the contribution of age and disease variables to the outcome of untreated patients with acute myeloid leukemia (AML) receiving varying intensive induction chemotherapy.

Patients and Methods
Patients 16 to 85 years of age with primary AML, known karyotype, and uniform postremission chemotherapy enrolled onto two consecutive trials were eligible and were randomly assigned to induction either with a standard-dose (cytarabine, daunorubicin, and 6-thioguanine) and a high-dose (cytarabine and mitoxantrone) combination, or with two courses of the high-dose combination. Subgroups were defined by karyotype, nucleophosmin and FLT3 mutation, WBC count, serum lactate dehydrogenase, and residual blasts.

Results
In 1,284 patients, the overall survival at 4 years in those younger and older than 60 years was 37% versus 16% (P < .001) and the ongoing remission duration was 46% versus 22% (P < .001). Similar age-related differences in outcome were found for all defined subgroups. No difference in outcome according to randomly assigned treatment regimen was observed in any age group or prognostic subset. Regarding prognostic subgroups, molecular factors were also considered.

Conclusion
Under harmonized conditions, older and younger patients with AML show modest differences in their risk profiles and equally no dose response to intensified chemotherapy. Their observed fundamental difference in outcome across all subgroups remains unexplained. Further molecular investigation may elucidate the age effect in AML and identify new targets.

Keywords
Acute myeloid leukemia, age, chemotherapy, induction therapy, outcome, survival.

INTRODUCTION

In acute myeloid leukemia (AML), some two thirds of patients are now 60 years of age or older.1,2 Even in multicenter trials, the proportion of older patients has increased. Thus in the 1981 study by the German AML Cooperative Group, patients older than 60 years accounted for 25% of patients;3 the percentage of patients in this age group reached 53% in the 1999 study.4 Compared with the gradual improvements achieved in younger patients, however, the therapeutic outcome shows a lack of progress in older patients.5,6

After earlier investigations failed to support attenuation strategies,5 the present project aimed to determine whether outcome in AML can be improved by intensification of induction chemotherapy and whether intensification benefits particular prognostic groups among younger and older patients, such as groups recently defined according to mutations of the nucleophosmin (NPM1) gene and the Fms-like tyrosine kinase length mutation in the juxtamembrane domain (FLT3-LM).8-10 To answer these questions, the data of two consecutive prospective randomized trials by the German AML Cooperative Group were evaluated. For maximum homogeneity, only patients with primary AML whose leukemic cell karyotype was known and who were assigned to the uniform prolonged maintenance chemotherapy were considered.

© 2008 by American Society of Clinical Oncology

...
considered in present analysis. According to the chromosomal findings, the rate of adequate cytogenetics was 66% in the 1992 trial and 97% in the 1999 trial. Only patients with known karyotypes were included in the 1999 trial, present analysis is restricted to patients with primary AML in both trials. The trials were approved by the ethics committees of the participating centers and were conducted in accordance with the Declaration of Helsinki. Written informed consent was given by all participants.

Prognostic Factors

At diagnosis, samples of bone marrow aspirates were examined for chromosomal abnormalities using standard banding techniques and classified according to the International System for Human Cytogenetic Nomenclature. The rate of adequate cytogenetics was 66% in the 1992 trial and 97% in the 1999 trial. Only patients with known karyotypes were considered in present analysis. According to the chromosomal findings, the individual leukemias were classified into three cytogenetic groups, with subdivisions into intermediate-normal and intermediate-other karyotype, as well as unfavorable-complex and unfavorable-other karyotype (Table 1). A sample of 396 patients with normal karyotype representative in outcome for this cytogenetic groups was characterized for mutations of the NPM1 gene and FLT3-LM by methods described. Other prognostic factors evaluated included WBC count, dichotomized at $20 \times 10^9/\mu L$; serum lactate dehydrogenase (LDH), a proven risk factor in high-grade lymphoma, testicular cancer, and AML; and FLT3-LM dichotomized at 700 U/L and blasts in the bone marrow 1 week after the first induction course, as proving a highly significant independent prognostic factor in a previous study.

Study Design and Chemotherapy

The standard version of induction treatment (TAD-HAM) started with cytarabine 100 mg/m$^2$ per day by continuous intravenous (IV) infusion on days 1 and 2 and by 30-minute IV infusions every 12 hours on days 3 through 8, daunorubicin 60 mg/m$^2$ by 60-minute IV infusion on days 3, 4, and 5, and 6-thioguanine 100 mg/m$^2$ orally every 12 hours on days 3 through 9 (TAD). The second induction course combined cytarabine 3 g (in patients $<60$ years of age) or 1 g (in patients $\geq 60$ years of age) by 3-hour IV infusion every 12 hours on days 1 through 3, with mitoxantrone 10 mg/m$^2$ by 60-minute IV infusions on days 3 through 5 (HAM). The second induction course was given to all patients younger than 60 years and, among patients 60 years and older, to those with 5% or more residual blasts in their bone marrow on day 16. After achieving complete remission, all patients received consolidation by one course of TAD. For maintenance treatment, patients received monthly courses of cytarabine 100 mg/m$^2$ with subcutaneous injections every 12 hours on days 1 through 5, and as second agent from course to course, either daunorubicin 45 mg/m$^2$ by 60-minute IV infusion on days 3 and 4, 6-thioguanine 100 mg/m$^2$ orally every 12 hours on days 1 through 5, or cyclophosphamide 1 g/m$^2$ per day by continuous IV infusion on days 1 through 5 (HAM).
by IV injection on day 3, with the second agent added in a rotating sequence. Maintenance continued for 3 years, and dose reductions by 50% were done after critical nadirs in absolute neutrophils of less than 500/μL or platelets of less than 20 × 10^3/μL were observed. For the intensified version of induction treatment (HAM-HAM), both induction courses consisted of the high-dose cytarabine/mitoxantrone combination described above, whereas the TAD consolidation and maintenance was as after the standard version of induction. Only patients assigned to the uniform maintenance regimen were considered for the present analysis. Patients randomly assigned to other treatment modalities, such as intensified consolidation instead of maintenance or autologous stem-cell transplantation, were not included in the present analysis (Fig 2). Allogeneic stem-cell transplantation in first remission was applied to patients younger than 60 years with histocompatible siblings in both trials. At 26 of the 47 centers within the 1999 trial, half of the patients were randomly assigned to receive granulocyte colony-stimulating factor by daily subcutaneous injections at 47 centers within the 1999 trial, half of the patients were randomly assigned to receive granulocyte colony-stimulating factor by daily subcutaneous injections of 150 μg/m² from 48 hours before until the last dose of each chemotherapy course during the first year. Assignment to granulocyte colony-stimulating factor did not affect the outcome and was accepted for present analysis.

**Statistical Analysis**

The primary objective of the present study was to determine the effect of intensified induction chemotherapy on patient outcome. Among the criteria of outcome, complete remission (CR) was defined as cellular marrow with less than 5% blasts and peripheral blood with at least 1.5 × 10^9/L of neutrophils and 100 × 10^9/L platelets. Survival was measured from treatment initiation to death, remission duration was measured from achievement of complete remission criteria until relapse, and relapse-free survival was measured from achievement of complete remission until relapse or death in remission. As part of the protocol, allogeneic stem-cell transplantation (12% of patients < 60 years of age) remained uncensored, because censoring had no major influence on the results. The outcome criteria were evaluated according to intention-to-treat. Significance were calculated for response rates by χ² test and for survival and remission duration by the log-rank test. Potential prognostic factors were tested using the Cox proportional hazards model, including the dichotomized variables of age (≥ 60 vs < 60 years), karyotype (favorable vs other; unfavorable vs other), normal karyotype with presence of nucleophosmin (NPM1) mutation in absence of FLT3-LM (+/-) versus other combinations of the two mutations (+/+ or -/- or +/-), day 16 bone marrow blasts (≥ 10% v < 10%), LDH (> 700 U/L or ≤ 700 U/L), and WBC (≥ 20 × 10^9/L v ≤ 20 × 10^9/L). The comparator groups were the respective other karyotypes and counterparts of the dichotomized variables. The study adhered to the revised recommendations of the International Working Group for Standardization in AML.

**RESULTS**

**Patient Population**

A total of 2,776 patients (age < 60 years, n = 1,440; age ≥ 60 years, n = 1,336; Fig 1) entered the 1992 and 1999 trials between January 1993 and November 2005. In the entire patient population, the CR rate was 63.0%, the overall survival at 4 years was 25.8%, the ongoing CR rate was 35.2%, and the relapse-free survival rate was 25.5%. To ensure maximum comparability, only patients with primary AML whose karyotype of leukemic bone marrow cells was known and who were assigned to a uniform postremission consolidation and maintenance chemotherapy were evaluated. A total of 505 patients were therefore excluded from present analysis as a result of having secondary AML. From the remaining 2,271 patients, 349 patients (15.4%) were excluded because of unknown karyotype. An additional 269 patients were not considered because they were assigned to intensive consolidation with high-dose cytarabine instead of maintenance, and 369 patients were excluded because they were assigned to autologous stem-cell transplantation (Figs 1 and 2). No
patients were excluded for other reasons. The analysis thus included 520 patients younger than 60 years and 764 patients older than 60 years, with no upper age limit.

Among the 1,284 patients included, 804 patients (353 patients younger and 451 patients older than 60 years) were randomly assigned to TAD-HAM induction and subsequent postremission TAD consolidation, followed by prolonged monthly maintenance. The other 480 patients (167 patients younger and 313 patients older than 60 years) were randomly assigned to HAM-HAM induction, equal TAD consolidation, and equal maintenance (Figs 1 and 2).

Table 1 lists patient characteristics. Although in older patients, karyotypes and day 16 blasts were more unfavorable, WBC counts and LDH were lower than in younger patients. Similar frequencies between the two age groups are found in the more favorable (+/-) and the more unfavorable (+/-, -/-, -/+ associations of the NPM1 mutation and FLT3-LM in case of normal karyotype.

**Drug Delivery**

By the protocol for the induction treatment, HAM as second course was given to 88.1% of all younger patients and 37.3% of those older patients with 5% or more residual bone marrow blasts. Among patients in remission, 82.6% younger and 79.1% older patients received TAD consolidation. Fifty-eight percent of younger and 57.6% of older patients proceeded to maintenance treatment. Exclusions from consolidation or maintenance were due to relapse, toxicity, allogeneic stem-cell transplantation, or other reasons. The delivery of maintenance followed a monthly schedule, with necessary delays and dose reductions according to grade and duration of cytopenia. Thus the adaptions of maintenance were strongly dependent on the stability of remission and development of relapse. Among the patients remaining in remission for 3 years or more, 86% continued with maintenance for at least 30 months.

**Outcome of Therapy by Randomization for Induction**

Among the older patients, 59.6% achieved CR, 59.9% in the TAD-HAM arm and 59.1% in the HAM-HAM arm. Accordingly, 24.4% and 27.8% of older patients in the TAD-HAM and HAM-HAM arms remained with resistant leukemia, and 15.7% and 13.1% succumbed to early or hypoplastic death, respectively ($P = .412$). Among younger patients, 70.4% achieved CR, 71.1% in the TAD-HAM arm and 68.9% in the HAM-HAM arm. Accordingly, 16.4% and 20.4% of younger patients in the TAD-HAM and HAM-HAM arms remained with resistant leukemia, and 12.4% and 10.8% succumbed to early or hypoplastic death, respectively ($P = .512$).

Figure 3 shows Kaplan-Meier estimates of overall survival and remission duration by randomization for induction in older compared with younger patients. Although older patients show inferior outcome, there is no dose response in either age group.

**Multivariate Analysis of Prognostic Factors**

Table 2 lists the independent prognostic factors and their significance related to major therapeutic end points. The strongest factors predicting overall survival were unfavorable karyotype, older age, high day 16 blasts, and favorable karyotype.

Table 3 analyzes patients with normal karyotype and their prognostic factors, including mutations of the NPM1 and FLT3 genes. In this large subgroup, the most important risk factors predicting overall

### Table 2. Multivariate Analysis of Prognostic Factors Including All Patients

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Complete Remission</th>
<th>Overall Survival</th>
<th>Remission Duration</th>
<th>Relapse-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>P</td>
<td>Hazard Ratio</td>
<td>P</td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>1.831</td>
<td>&lt;.001</td>
<td>1.633</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Favorable karyotype</td>
<td>0.747</td>
<td>.181</td>
<td>0.672</td>
<td>.007</td>
</tr>
<tr>
<td>Unfavorable karyotype</td>
<td>2.754</td>
<td>&lt;.001</td>
<td>2.270</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Day 16 bone marrow blasts ≥ 10%</td>
<td>1.576</td>
<td>&lt;.001</td>
<td>1.255</td>
<td>.046</td>
</tr>
<tr>
<td>WBC count &gt; 20 × 10^9/µL</td>
<td>1.117</td>
<td>.412</td>
<td>1.171</td>
<td>.585</td>
</tr>
<tr>
<td>Serum LDH &gt; 700 U/L</td>
<td>1.174</td>
<td>.281</td>
<td>1.212</td>
<td>.037</td>
</tr>
</tbody>
</table>

NOTE. P values were calculated by the logistic or Cox regression analysis (Wald test). Odds and hazard ratios give the probabilities to not achieve complete remission, to die, to experience relapse, and to experience relapse or die in complete remission.

### Table 3. Multivariate Analysis of Prognostic Factors in Patients With Normal Karyotype and Complete NPM1/FLT3 Mutation Status

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Complete Remission</th>
<th>Overall Survival</th>
<th>Remission Duration</th>
<th>Relapse-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>P</td>
<td>Hazard Ratio</td>
<td>P</td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>1.581</td>
<td>.067</td>
<td>1.448</td>
<td>.018</td>
</tr>
<tr>
<td>Mutation NPM1+ and FLT3-ITD−</td>
<td>0.500</td>
<td>.077</td>
<td>0.496</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Day 16 bone marrow blasts ≥ 10%</td>
<td>1.540</td>
<td>.004</td>
<td>1.540</td>
<td>.004</td>
</tr>
<tr>
<td>WBC count &gt; 20 × 10^9/µL</td>
<td>1.017</td>
<td>.946</td>
<td>1.371</td>
<td>.049</td>
</tr>
<tr>
<td>Serum LDH &gt; 700 U/L</td>
<td>1.039</td>
<td>.891</td>
<td>1.297</td>
<td>.122</td>
</tr>
</tbody>
</table>

NOTE. P values were calculated by the logistic or Cox regression analysis (Wald test). Odds and hazard ratios give the probabilities to not achieve complete remission, to die, to experience relapse, and to experience relapse or die in complete remission.

Abbreviations: NPM1, nucleophosmin 1 gene; FLT3, Fms-like tyrosine kinase gene (length mutation); LDH, lactate dehydrogenase.
survival were the sole mutation of NPM1, high day 16 blasts, and older age.

**Outcome by Randomization in Prognostic Groups**

On the basis of the multivariate analysis, prognostic subgroups were defined according to karyotype, NPM1/FLT3 mutation status, LDH, WBC, and day 16 bone marrow blasts (Tables 1, 2, and 3). As in the entire population, there was no significant difference in the overall survival and remission duration between the TAD-HAM and the HAM-HAM induction regimen in any subgroup, neither in older nor in younger patients (Appendix Tables A1 and A2, online only).

**Outcome by Age in Prognostic Groups**

As in the overall patient population (Fig 3), there is an inferior survival and remission duration in the older versus younger patients in all subgroups defined by karyotype (Fig 4), NPM1/FLT3 mutation status (Fig 5), WBC, LDH, and day 16 bone marrow blasts (Fig 6; Appendix Table A3, online only).

---

![Graphs showing survival and remission duration by age and karyotype](image-url)
Outcome in Excluded Patients

The outcome by randomization and by age in patients with secondary AML or unknown karyotype was similar to that in the defined prognostic groups (data not shown).

DISCUSSION

The present evaluation of 1,284 patients spanning all ages from 16 to 85 years, restricted to primary AML and identical postremission treatment, confirmed the inferiority of older age in terms of therapeutic outcome. Patients older than 60 years achieved a survival only half that of younger patients as a result of less frequent remissions, more frequent resistant disease, and more frequent and earlier relapses. These differences were equally seen in all prognostic subgroups defined by cytogenetics, NPM1/FLT3 mutation status, WBC, LDH, and early blast clearance.

The disease seems resistant even against intensification of chemotherapy. In fact, the HAM-HAM version of induction represents a marked intensification against the TAD-HAM version, even taking an age adaption in the patients older than 60 years into account. As we previously reported, double induction by TAD-HAM versus TAD-TAD produced a higher CR rate ($P = .004$) and longer event-free ($P = .012$) and overall survival ($P = .009$) in patients younger than 60 years with poor prognosis.\(^{15}\) The recovery time of neutrophils and platelets was a median of 16 days after TAD-TAD and 20 days after TAD-HAM ($P = .0001$).\(^{15}\) Regarding patients older than 60 years, the CR rate after the first induction course was 30% in the TAD-HAM arm and 36% in the HAM-HAM arm ($P = .049$). Older patients with a high LDH showed a trend to longer survival from HAM-HAM induction ($P = .024$).\(^4\) Although the TAD-HAM and the HAM-HAM induction regimens differ markedly in their intensities, the overall survival and remission duration could not be further improved in either age group. This was equally found across all prognostic subgroups, defined by cytogenetics, NPM1/FLT3 mutation status, WBC, LDH, and early blast clearance. Thus the general absence of a dose response suggests that once a certain intensity has been reached, a further intensification will not further improve the antileukemic potential of chemotherapy.

The inherently poor outcome in older patients with AML is incompletely understood. Prognostic factors commonly discussed, such as a preceding myelodysplastic syndrome or cytotoxic treatment,\(^{20,21}\) were excluded here. Beyond the negative history, chromosomal abnormalities described as typical for secondary AML\(^{22-24}\) and ranging in the subset of unfavorable karyotype were only modestly increased in the older compared with the younger patients (24% vs 18%). In other series, an expression of the multidrug resistance gene or P glycoprotein was shown in 71% of older and 35% of younger patients\(^{25}\) and was associated with poorer response,\(^{26}\) A relationship to the relapse rate or relapse-free survival was not found\(^{25}\) and has not
been substantiated thus far. Moreover, the effect of high-dose cytarabine seems to not be affected by multidrug resistance.\(^27\) Among other risk factors, morphologic dysplasia has not been confirmed as an independent factor in AML.\(^28,29\) The mixed lineage leukemia gene partial tandem duplication was infrequent overall.\(^30\) The frequent FLT3 gene mutations occurred in 23% to 32% of patients,\(^12,16,31-33\) who were rather younger.\(^12\)

When comparing 1,612 patients younger than 55 years with an older population of 1,065 patients in two consecutive British trials,\(^34\) favorable karyotypes were found in 24% versus 7% and unfavorable karyotypes in 10% versus 19%, respectively, and thus did not characterize the bulk of older patients. Even smaller differences of only 16% versus 7% favorable karyotypes and 18% versus 24% unfavorable karyotypes in younger and older patients, respectively, were found in the present analysis, which, unlike the British trials, divided the age groups at 60 years and excluded children. In five separate trials, two in younger and three in older patients, the Southwest Oncology Group treated 968 patients with primary and secondary AML by differing regimens. In four groups at increasing levels of age, an increasingly poor performance status, unfavorable cytogenetics, and deteriorating outcome within the cytogenetic groups were found.\(^6\) In the context of age-related disease biology, an increased WBC count has commonly

![Diagram](image_url)

**Fig 6.** (A) Overall survival and (B) remission duration in younger (age 16 to 59 years) and older (age 60+ years) patients predicted by WBC ≤20,000/μL, serum lactate dehydrogenase (LDH) ≤700 U/L, and day 16 bone marrow blasts less than 10%.
been considered an adverse prognostic factor.35-39 However, a lower WBC was found in older patients, and the authors assumed older age AML was a less proliferative disease.9 Even restricted to primary AML, present analysis supports this hypothesis by showing significantly lower WBC as well as LDH in the older than in the younger patients.

Recently, cytoplasmic dislocation of nucleophosmin (NPM) with mutation of the NPM1 gene has been described as being associated with normal karyotype and responsiveness to induction chemotherapy.8 In the trials of two AML study groups, mutant NPM was detected in half of the patients with normal karyotype and frequently occurred together with FLT3 length mutations. NPM1 mutation significantly predicted for favorable overall survival and relapse-free survival if FLT3-LM was absent,10 essentially confirmed by other groups.40-43 In the two studies including patients younger and older than 60 years, no relation of NPM1 mutation to age was described.44 Among patients with normal karyotype in the present analysis, the favorable co-expression of mutant NPM1 and normal FLT3 was found at comparable frequencies (37% and 33%) in younger and older patients, respectively, and equally predicted for superior survival and remission duration.

Considering postremission treatment, others have shown no benefit from intermediate or high-dose chemotherapy in older as compared with younger patients.9 Prolonged maintenance as the preferred postremission chemotherapy in the present study produced a relapse-free survival similar to that achieved with intensive consolidation in younger and older patients.16

In conclusion, as new findings in the present study restricted to homogeneous and comparable patient populations, the outcome in older (60+ years) patients is inferior to that of younger (16 to 59 years) patients equally across prognostic groups defined by cytogenetics, NPM1/FLT3 mutation, WBC, LDH, and early blast clearance. Also, there is no dose response to two different intensive induction regimens in either age group. The difference in outcome is not explained by the modest differences in the defined risk profiles between older and younger patients. Recently described mutations in the FLT3, NPM1, CEBPA, and MLL genes and expression changes in the BAALC and ERG genes have not shown age-related differences.44 Further gene expression profiling may elucidate the age effect in AML and detect new therapeutic targets.

REFERENCES

16. Büchner T, Hiddemann W, Berdel WE, et al: 6-thioguanine, cytarabine, and daunorubicin (TAD) and high-dose cytarabine and mitoxantrone (HAM) for induction, TAD for consolidation, and either prolonged maintenance by reduced monthly TAD or prolonged maintenance by sequential HAM in adult patients at all ages with de novo acute myeloid leukemia (AML): A

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Thomas Büchner, Wolfgang E. Berdel, Claudia Haferlach, Torsten Haferlach, Carsten Müller-Tidow, Georg Maschmeyer, Eva Lengfelder, Maria-Cristina Sauerland, Bernhard Wörnmann, Wolfgang Hiddemann

Administrative support: Thomas Büchner, Wolfgang E. Berdel

Provision of study materials or patients: Thomas Büchner, Wolfgang E. Berdel, Claudia Haferlach, Torsten Haferlach, Susanne Schnittger, Jan Braess, Karsten Spiekermann, Joachim Kienast, Peter Staub, Andreas Grünseisen, Wolfgang Kern, Albrecht Reichle, Carlo Aul, Eva Lengfelder, Bernhard Wörnmann, Wolfgang Hiddemann

Collection and assembly of data: Thomas Büchner, Claudia Haferlach, Torsten Haferlach, Maria-Cristina Sauerland, Achim Heinecke

Data analysis and interpretation: Thomas Büchner, Wolfgang E. Berdel, Claudia Haferlach, Torsten Haferlach, Susanne Schnittger, Carsten Müller-Tidow, Jan Braess, Karsten Spiekermann, Joachim Kienast, Peter Staub, Andreas Grünseisen, Wolfgang Kern, Albrecht Reichle, Georg Maschmeyer, Carlo Aul, Eva Lengfelder, Maria-Cristina Sauerland, Achim Heinecke, Bernhard Wörnmann, Wolfgang Hiddemann

Manuscript writing: Thomas Büchner, Wolfgang E. Berdel, Torsten Haferlach

Final approval of manuscript: Thomas Büchner, Wolfgang E. Berdel, Claudia Haferlach, Torsten Haferlach, Susanne Schnittger, Carsten Müller-Tidow, Jan Braess, Karsten Spiekermann, Joachim Kienast, Peter Staub, Andreas Grünseisen, Wolfgang Kern, Albrecht Reichle, Georg Maschmeyer, Carlo Aul, Eva Lengfelder, Maria-Cristina Sauerland, Achim Heinecke, Bernhard Wörnmann, Wolfgang Hiddemann

Acknowledgment
We thank Birgit Mayerhofer for secretarial assistance.

www.jco.org © 2008 by American Society of Clinical Oncology 69