Symptomatic central nervous system involvement in adult patients with acute myeloid leukemia

Introduction: Acute myeloid leukemia (AML) rarely involves the central nervous system (CNS). Little is known about the clinical course in adult AML patients since most studies examined pediatric patients. Therefore, this study analyzed the data of patients treated in three prospective trials of the “Study Alliance Leukemia” (SAL) study group for CNS involvement. Methods: In all, 3,261 AML patients included in the prospective AML96, AML2003, and AML60+ trials of the SAL study group were analyzed. Symptomatic patients underwent cerebrospinal fluid (CSF) puncture and CNS involvement was diagnosed depending on morphology and/or flow cytometry of the CSF. Cytogenetic, molecular, clinical, and laboratory parameters were analyzed in order to identify risk factors. Results: A total of 55 patients had proven symptomatic CNS involvement. Significantly more patients revealed CNS involvement at relapse (34 patients, 2.9%) compared with first diagnosis (21 patients, 0.6%), p<0.001. CNS involvement at initial diagnosis had a significantly higher frequency in patients with complex aberrant karyotypes, high serum lactate dehydrogenase activity, French–American–British M5 subtype, FLT3–internal tandem duplication (ITD) mutations alone, and co-occurrence of a FLT3–ITD and NPM1 mutation. Furthermore, AML patients with CNS involvement at diagnosis had an inferior outcome compared with patients without CNS involvement even if treated with intrathecal chemotherapy with an overall survival of 11% versus 30% at 5 years, p=0.004. Conclusion: This study analyzed the largest data set of adult AML patients with proven CNS involvement reported so far. The data demonstrated very low prevalence of CNS involvement at initial diagnosis in adult patients with AML, and described new risk factors. In patients with risk factors, intense diagnostic and treatment strategies should be employed in the future. Keywords: Meningeal leukemia, CNS-involvement, cerebrospinal fluid, extramedullary leukemia

Introduction: In contrast to acute lymphoblastic leukemia, acute myeloid leukemia (AML) rarely involves the central nervous system (CNS) in adult patients while it is more common in pediatric AML patients.1,2 Therefore, routine diagnostic evaluation or prophylactic CNS therapy in adult AML is not performed, although some authors recommend a routine evaluation when hyperleukocytosis is present at diagnosis.3,4 Bojesen-Moller and Nielsen performed an autopsy study and found leukemic CNS infiltrates in 46% of all AML patients, which could point to higher rates of asymptomatic CNS involvement, but might be biased since the remission status of the studied patients was not approximated, and an autopsy study usually includes more patients with unfavorable and relapsed disease.5 However, symptoms of CNS involvement may develop later during disease progression or at relapse, which might influence the outcome. Furthermore, CNS involvement might
be diagnosed through the appearance of either leukemic blasts in the cerebrospinal fluid (CSF) and/or with intracerebral myeloid sarcoma or meningeal AML. Risk factors identified so far include high initial white blood cell (WBC) count in the peripheral blood and AML M5 French–American–British (FAB) morphology. Several treatment options such as cranial and/or neuro-axis irradiation and intrathecal therapy (ITC) with methotrexate (MTX) and/or cytosine arabinoside (Ara-C) and glucocorticoids along with systemic chemotherapy are widely accepted. Little is known regarding CNS involvement in adult AML and its impact on survival since most studies examined pediatric patients or only a limited number of patients. Therefore, the present study analyzed CNS involvement in patients with AML treated in the prospective AML96, AML2003, and AML60+ trials of the “Study Alliance Leukemia” (SAL) study group for a better understanding of this rare AML entity and to identify patient populations that are at increased risk for CNS disease. This report represents the largest cohort of AML patients analyzed with respect to CNS involvement to date.

**Patients and methods**

Between February 1996 and November 2009, 3,526 adult patients with non-acute promyelocytic leukemia AML were included in the prospective AML96, AML2003, and AML60+ trials of the SAL. The studies were approved by the ethics committees of the University of Dresden and all other participating centers. A list of participating centers and ethics committees can be found in the [Supplementary material](#). The protocols were in agreement with the Helsinki declaration and registered with NCT numbers 00180115 (AML96), 00180102 (AML2003), and 00180167 (AML60+). Written informed consent was obtained from all patients. Data were collected and certified by the SAL Data Center.

In the AML96 protocol, patients <60 years of age were treated with double induction chemotherapy including standard- and intermediate-dose mitoxantrone, Ara-C, etoposide, and amsacrine and stratified post-remission therapy in different cytogenetic risk groups. Intermediate risk patients with a human leukocyte antigen (HLA)-identical sibling donor were referred to allogeneic hematopoietic stem cell transplant (HSCT). High risk patients were referred to unrelated HLA-compatible allogeneic HSCT. Patients >60 years of age received double induction chemotherapy with daunorubicin and standard-dose Ara-C followed by consolidation therapy consisting of intermediate-dose Ara-C and amsacrine.

In the AML60+ trial, patients >60 years of age were included and randomized between the treatment arm of the AML96 study for elderly patients and induction with intermediate-dose Ara-C and mitoxantrone. Allogeneic HSCT was optional for fit patients.

The AML2003 trial included patients below the age of 61 years. Patients were randomized up-front in a two-by-two factorial design with the two factors high-dose Ara-C alone versus high-dose Ara-C plus mitoxantrone and amsacrine for consolidation and standard versus risk adapted intensified consolidation including early allogeneic HSCT during induction therapy and autologous HSCT. All patients received a 3+7 regimen with daunorubicin and Ara-C as induction chemotherapy.

In the presence of neurologic or psychiatric abnormalities, lumbar puncture was performed to confirm or exclude CNS involvement through microscopy and/or flow cytometry of the CSF in all three prospective trials. CNS disease was treated with ITC with MTX, Ara-C, and glucocorticoids. Treatment response and treatment outcome were defined according to the recommended consensus criteria. Data of proven extramedullary manifestations were available in 3,261 patients, which were included in this study. The patient characteristics are summarized in Table 1. The distributions of cytogenetic, molecular, clinical, and laboratory parameters were compared in order to identify risk factors for CNS involvement. The chi-square test was used for significance testing of comparisons in categorical variables and the Mann–Whitney U test for continuous variables. Kaplan–Meier method was used to estimate the overall survival (OS). Survival distributions were compared using the log-rank test.

**Results**

For this study, all 3,261 patients were analyzed with a median follow-up of 5.1 years. A total of 21 patients had CNS involvement at the time of initial presentation resulting in a prevalence of 0.6%. CNS involvement at AML relapse had a statistically higher incidence of 2.9% with 34 affected patients among 1,154 patients at relapse versus 21 of 3,261 patients at initial diagnosis (p=0.010).

Characteristics and outcome of CNS disease at initial diagnosis were further analyzed (Table 1). The majority of patients (n=18, 86%) had de novo AML. The median age of these patients was 54 years (range 22–77 years). Gender and age were equally distributed between patients with CNS involvement and patients without CNS involvement. Extramedullary AML other than CNS was present more frequently in patients with CNS involvement as compared to patients without CNS involvement (n=13, 62% vs n=344, 11%, p<0.001).
Significantly more patients with CNS involvement had FLT3–ITD mutations (n=8, 44% vs n=611, 21%, p=0.017) and when grouping FLT3–ITD and NPM1 mutations, there was a statistically significant higher occurrence of combined FLT3–ITD and NPM1 mutations in patients with CNS involvement as compared to those without CNS involvement (n=7, 44% vs n=335, 12%, p=0.002). Furthermore, patients with CNS involvement exhibited significantly higher levels of lactate dehydrogenase activity (LDH) (log U/l 2.81 vs 2.59, p=0.023) (base 10 logarithm), higher frequencies of FAB M5 morphology (n=8, 38% vs n=417, 13%, p=0.001) compared with patients without CNS involvement. When analyzing patients at initial diagnosis, complex aberrant karyotypes were significantly more frequent in patients with CNS involvement compared with those without CNS involvement (n=6, 29% vs n=398, 12%, p=0.025).

Fourteen of 21 patients with CNS involvement at initial diagnosis were treated with ITC. Survival and complete remission rates for these patients were analyzed. Patients with CNS involvement reached complete remission less frequently than patients without CNS involvement (n=10, 48% vs n=2,317, 72%, p=0.016), and had a significantly inferior outcome even if treated with ITC with an OS of 11% (95% confidence interval [CI], 0%–25%) versus 30% (95% CI, 28%–32%) at 5 years, p=0.004 (Figure 1).

### Table 1 Comparison of patients’ characteristics between AML patients with and without CNS involvement at diagnosis

<table>
<thead>
<tr>
<th>AML patients at diagnosis n=3,261</th>
<th>Patients with CNS involvement at initial diagnosis n=21</th>
<th>Patients without CNS involvement at initial diagnosis n=3,240</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML96, n</td>
<td>16</td>
<td>1,632</td>
<td></td>
</tr>
<tr>
<td>AML2003, n</td>
<td>3</td>
<td>1,156</td>
<td></td>
</tr>
<tr>
<td>AML60+, n</td>
<td>2</td>
<td>452</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12 (57)</td>
<td>1,630 (50)</td>
<td>0.496</td>
</tr>
<tr>
<td>Male</td>
<td>9 (43)</td>
<td>1,610 (50)</td>
<td></td>
</tr>
<tr>
<td><strong>Median age at diagnosis, years (range)</strong></td>
<td>54 (22–77)</td>
<td>57 (15–87)</td>
<td>0.904</td>
</tr>
<tr>
<td><strong>Median WBC log mean ¥10⁹/L (range)</strong></td>
<td>1.13 (0.14–2.41)</td>
<td>1.06 (0–2.67)</td>
<td>0.054</td>
</tr>
<tr>
<td><strong>Median platelets log mean ¥10⁹/L (range)</strong></td>
<td>1.9 (1.04–2.37)</td>
<td>1.72 (0–3.12)</td>
<td>0.334</td>
</tr>
<tr>
<td><strong>FAB classification at diagnosis, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>1 (5)</td>
<td>160 (5)</td>
<td>0.962</td>
</tr>
<tr>
<td>M1</td>
<td>4 (19)</td>
<td>702 (22)</td>
<td>0.754</td>
</tr>
<tr>
<td>M2</td>
<td>5 (24)</td>
<td>963 (30)</td>
<td>0.536</td>
</tr>
<tr>
<td>M4</td>
<td>3 (14)</td>
<td>509 (16)</td>
<td>0.843</td>
</tr>
<tr>
<td>M5</td>
<td>8 (38)</td>
<td>438 (14)</td>
<td>0.001</td>
</tr>
<tr>
<td>M6</td>
<td>0 (0)</td>
<td>103 (3)</td>
<td>0.404</td>
</tr>
<tr>
<td>M7</td>
<td>0 (0)</td>
<td>22 (1)</td>
<td>0.703</td>
</tr>
<tr>
<td><strong>Complex aberrant cytogenetic karyotype, n (%)</strong></td>
<td>6 (29)</td>
<td>398 (12)</td>
<td>0.025</td>
</tr>
<tr>
<td><strong>LDH log U/L (range)</strong></td>
<td>2.81 (2.16–3.86)</td>
<td>2.56 (0.38–4.22)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Extramedullary AML other than CNS, n (%)</strong></td>
<td>13 (62)</td>
<td>344 (11)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>FLT3–ITD positive, n (%)</strong></td>
<td>8 (44)</td>
<td>611 (21)</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>NPM1 mut, n (%)</strong></td>
<td>8 (50)</td>
<td>834 (30)</td>
<td>0.078</td>
</tr>
<tr>
<td><strong>FLT3–ITD/NPM1, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLT3–ITD neg/NPM1 neg</td>
<td>7 (44)</td>
<td>1,668 (60)</td>
<td></td>
</tr>
<tr>
<td>FLT3–ITD neg/NPM1 pos</td>
<td>1 (6)</td>
<td>265 (10)</td>
<td>0.002</td>
</tr>
<tr>
<td>FLT3–ITD pos/NPM1 neg</td>
<td>1 (6)</td>
<td>494 (18)</td>
<td></td>
</tr>
<tr>
<td>FLT3–ITD pos/NPM1 pos</td>
<td>7 (44)</td>
<td>335 (12)</td>
<td></td>
</tr>
<tr>
<td><strong>Complete remission (including CRi), n (%)</strong></td>
<td>10 (48)</td>
<td>2,317 (72)</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>Allogeneic stem cell transplantation, n (%)</strong></td>
<td>6 (29)</td>
<td>556 (17)</td>
<td>0.045</td>
</tr>
</tbody>
</table>

**Note:** * Calculated as base 10 logarithms.

**Abbreviations:** AML, acute myeloid leukemia; CNS, central nervous system; LDH, lactate dehydrogenase activity; ITD, internal tandem duplication; FAB, French–American–British; NA, not applicable; pos, positive; neg, negative; mut, mutation; WBC, white blood cell.

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kemia, used imaging studies with magnetic resonance imaging
in pediatric patients while others included promyelocytic leu-
reports could be the fact that some of these studies were done
involvement in parallel to cranial irradiation and/or ITC
without CNS symptoms. Systemic therapy for isolated CNS
involvement may remain asymptomatic. Diagnostic lumbar
puncture or prophylactic ITC is not routinely recommended
in patients with proven CNS involvement reported so far. An over-
all prevalence of 0.6% was found at initial diagnosis which is
lower than previously reported prevalence ranging between 2%
and 8%.1,24,25 One possible reason of higher rates in the earlier
reports could be the fact that some of these studies were done
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sarcoma, meningeal AML, or simply inflammatory enhance-
ment. Furthermore, the data from the present analysis reflect
only the patients in whom manifestation of CNS involvement
was clinically apparent due to neurological and/or psychiatric
symptoms. Thus, this could implicate that the real prevalence
including asymptomatic CNS involvement is higher, although
another study suggested that this might not be the case.29

In this analysis, symptomatic CNS involvement was
frequently accompanied by other extramedullary AML
manifestations and higher prevalence of FLT3–ITD mutations,
wheras NPM1 mutations alone had no significant higher
incidence in these patients. As previously shown, FAB M5
morphology, complex aberrant karyotype, higher LDH levels,
and higher WBC count at diagnosis represent risk factors for
CNS involvement.3,8,13,25 Interestingly, other studies showed an
association of CNS involvement in AML with certain cytoge-
etic abnormalities such as inv(16), del(5q), del(7q), trisomy
of chromosome 8, t(8;21), and abnormalities of chromosome
11q23, which could not be confirmed for patients with CNS
involvement at the initial diagnosis of AML.25,30,31

However, upon extending the data analysis by including
also CNS involvement of AML at relapse, statistically sig-
nificant higher incidence of CNS involvement was confirmed
for patients with trisomy of chromosome 8, trisomy of chro-
mosome 22, t(9;11), t(6;11), and complex karyotype. The study
could not confirm a higher prevalence for patients with
t(8;21), inv(16), monosomy of chromosome 5, or monosomy
of chromosome 7 (Table 2). In total, abnormalities of chro-
omosome 11q23 were evident in 20% of all AML patients with
CNS involvement either at initial diagnosis or at relapse of
CNS involvement (n=11/55). In 7 patients 11q23 abnormalities
were only detected using FISH analysis (Fluorescence in situ
hybridization). In these cases the 11q23 translocation was
cryptic by karyotyping. This reflects a higher prevalence of
11q23 abnormalities than the estimated 6% in AML with a
higher occurrence in myelomonocytic AML.32,33 Hence, data
from the present analysis confirm the previously reported
higher occurrence of 11q23 abnormalities of patients with
CNS disease as reported by others recently.13,25,34

The impact of CNS involvement on long-term treatment
outcome has been discussed controversially.3,8,10,21 Recently,
Shihadeh et al suggested that adult AML patients with CNS
involvement have poor OS.25 The present study could confirm
this finding based on the largest number of patients with
CNS involvement and define further risk factors (FLT3–ITD
mutations, complex aberrant karyotypes) that might help to
identify AML patients at risk for CNS involvement (Figure 2).
However, due to the low frequency and low ITC chemother-
apy-initiation at diagnosis in the three reported AML trials,
differently sized patient cohorts have been compared and the
statistical impact must be interpreted carefully. In summary,
this analysis suggests a very low frequency of symptomatic
CNS AML involvement in adults. Because of the obviously
poor prognosis of CNS involvement, screening for risk factors
of CNS involvement at diagnosis in symptomatic AML
patients with suspicion for CNS involvement may be useful
to identify a patient population benefiting from intensified
treatment strategies in the future.

Discussion

AML rarely involves the CNS in adults and there are only
a few published studies with controversial results.9,20,21 CNS
involvement may remain asymptomatic. Diagnostic lumbar
puncture or prophylactic ITC is not routinely recommended
without CNS symptoms. Systemic therapy for isolated CNS
involvement in parallel to cranial irradiation and/or ITC
seems to be necessary in order to avoid marrow relapse.22,23

This study analyzes the largest data set of adult AML
patients with proven CNS involvement reported so far. An over-
all prevalence of 0.6% was found at initial diagnosis which is
lower than previously reported prevalence ranging between 2%
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poor prognosis of CNS involvement, screening for risk factors
of CNS involvement at diagnosis in symptomatic AML
patients with suspicion for CNS involvement may be useful
to identify a patient population benefiting from intensified
treatment strategies in the future.
Table 2 Comparison of cytogenetic profile between AML patients with and without CNS involvement at diagnosis or relapse

<table>
<thead>
<tr>
<th>Cytogenetic profile</th>
<th>AML patients at diagnosis</th>
<th>Patients with CNS involvement at initial diagnosis and relapse</th>
<th>Patients without CNS involvement at any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal karyotype, n (%)</td>
<td>16 (31)</td>
<td>1,472 (50)</td>
<td>0.158</td>
</tr>
<tr>
<td>Trisomy 8, n (%)</td>
<td>10 (21)</td>
<td>254 (8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Trisomy 22, n (%)</td>
<td>3 (6)</td>
<td>62 (2)</td>
<td>0.034</td>
</tr>
<tr>
<td>Trisomy 11, n (%)</td>
<td>1 (2)</td>
<td>35 (1)</td>
<td>0.514</td>
</tr>
<tr>
<td>Trisomy 13, n (%)</td>
<td>1 (2)</td>
<td>42 (1)</td>
<td>0.641</td>
</tr>
<tr>
<td>Trisomy 21, n (%)</td>
<td>2 (4)</td>
<td>69 (2)</td>
<td>0.343</td>
</tr>
<tr>
<td>Monosomy 5, n (%)</td>
<td>0 (0)</td>
<td>26 (1)</td>
<td>0.531</td>
</tr>
<tr>
<td>Monosomy 7, n (%)</td>
<td>0 (0)</td>
<td>144 (4)</td>
<td>0.133</td>
</tr>
<tr>
<td>t(3;3), n (%)</td>
<td>0 (0)</td>
<td>8 (1)</td>
<td>0.729</td>
</tr>
<tr>
<td>t(1;17), n (%)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0.903</td>
</tr>
<tr>
<td>t(6;11), n (%)</td>
<td>1 (2)</td>
<td>6 (0)</td>
<td>0.005</td>
</tr>
<tr>
<td>t(8;21), n (%)</td>
<td>2 (4)</td>
<td>128 (4)</td>
<td>0.951</td>
</tr>
<tr>
<td>t(9;11), n (%)</td>
<td>3 (6)</td>
<td>41 (1)</td>
<td>0.003</td>
</tr>
<tr>
<td>t(6;9), n (%)</td>
<td>0 (0)</td>
<td>22 (1)</td>
<td>0.565</td>
</tr>
<tr>
<td>t(9;22), n (%)</td>
<td>0 (0)</td>
<td>7 (1)</td>
<td>0.746</td>
</tr>
<tr>
<td>t(11;19), n (%)</td>
<td>0 (0)</td>
<td>16 (1)</td>
<td>0.624</td>
</tr>
<tr>
<td>inv(16), n (%)</td>
<td>3 (6)</td>
<td>150 (5)</td>
<td>0.610</td>
</tr>
<tr>
<td>inv(3) (q21q26)</td>
<td>0 (0)</td>
<td>20 (1)</td>
<td>0.583</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; CNS, central nervous system.

Figure 2 Risk factors for symptomatic AML patients with potential CNS involvement at initial diagnosis of AML.
Abbreviations: AML, acute myeloid leukemia; CNS, central nervous system; LDH, lactate dehydrogenase activity; ITD, internal tandem duplication; FAB, French–American–British.

Acknowledgments
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Disclosure
The authors report no conflicts of interests in this work.

References


