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HATİME ARZU YAŞAR
OLGU ERKİN ÇINAR
NUR YAZDALI KÖYLÜ
İBRAHİM BARIŞTA
HAKAN GÖKER

See next page for additional authors

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Recommended Citation
YAŞAR, HATİME ARZU; ÇINAR, OLGU ERKİN; KÖYLÜ, NUR YAZDALI; BARIŞTA, İBRAHİM; GÖKER, HAKAN; and BÜYÜKAŞIK, YAHYA (2021) "Central nervous system involvement in patients with acute myeloid leukemia," Turkish Journal of Medical Sciences: Vol. 51: No. 5, Article 16. https://doi.org/10.3906/sag-2103-127
Available at: https://journals.tubitak.gov.tr/medical/vol51/iss5/16

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Authors
HATİME ARZU YAŞAR, OLGU ERKİN ÇİNDAR, NUR YAZDALİ KÖYLÜ, İBRAHİM BARIŞTA, HAKAN GÖKER, and YAHYA BÜYÜKAŞIK

This article is available in Turkish Journal of Medical Sciences: https://journals.tubitak.gov.tr/medical/vol51/iss5/16
Central nervous system involvement in patients with acute myeloid leukemia

Hatime Arzu YAŞAR1*, Olgu Erkin ÇINAR2, Nur YAZDALI KÖYLÜ1, İbrahim BARIŞTA1, Hakan GÖKER2, Yahya BÜYÜKAŞIK2

1Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey
2Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey
3Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey

Introduction
Acute myeloid leukemia (AML) was the most frequent acute leukemia in adult patients. The incidence is around 3–5 per 100,000 [1]. The central nervous system (CNS) involvement in patients with AML is rare and not identified certainly. Therefore, baseline screening is not recommended for the patients without symptoms [2,3]. Clinically symptomatic CNS involvement is not common after treatment. The factors related to CNS involvement are reported as monocytic component predominant AML, systemic relapse of acute promyelocytic leukemia (APL), presence of inversion 16, chromosome 11 anomalies, hyperleukocytosis, lactate dehydrogenase (LDH) elevation, and FLT3–internal tandem duplication (ITD) mutations [4–9]. Leukemic cells expressing CD56 adhesion molecule on cell surface were also investigated as a risk factor for CNS involvement [10,11]. It was found that CNS involvement in patients with AML usually presents as leptomeningeal involvement, but it may also rarely present as a mass in the brain parenchyma in acute myelomonocytic leukemia (French-American-British, FAB, AML-M4 subtype) patients with inv(16)(p13q22) or del(16)(q22) inversion 16 (+) AML [5].

In this study, we aimed to determine the incidence, type, risk factors, and prognosis of CNS involvement in patients with AML.
flow cytometric analysis. Organomegaly, lymphadenopathy, gum hypertrophy, and histologically documented any tissue involvement were evaluated as extramedullary involvement. The diagnosis of CNS involvement was done by radiological evaluations in patients with suspicious neurological symptoms. Cerebrospinal fluid analysis, biopsies, and ophthalmological examinations were also performed when clinically indicated. In the literature, data about CNS involvement in adult AML is limited, probably due to the low patient number (Figure).

3. Results

3.1. Patients

Five hundred forty-eight patients were included in the study. A total of 58% of them were male (n = 318) and 42% were female (n = 230). The median age was 50.9 (18.3–88.1.0). The median follow-up duration of the surviving patients was 32.3 (0.03–358.7) months. Patient characteristics are presented in Table 1.

3.2. Incidence and type of CNS involvement

The incidence of CNS involvement in patients with AML was 2.4% (n = 13) at the time of diagnosis. Twelve cases developed CNS disease during follow-up in spite of no involvement at the time of diagnosis. So, the frequency of CNS involvement at the time of diagnosis or follow-up was 4.6% (n = 25).

Parenchymal involvement was seen in 5 patients, leptomeningeal involvement was seen in 11 patients. Three patients had both leptomeningeal and parenchymal involvement, and 6 patients had optic nerve or ocular involvement. Cranial palsy, mental alteration, head and neck pain, seizure, paralysis, blurred vision, and loss of balance were seen as symptoms in patients with CNS involvement.

3.3. Risk factors for CNS involvement

Univariate and multivariate analyzes for CNS involvement at diagnosis, at relapse and anytime are summarized in Table 2. In the univariate analysis, age, white blood cell, lactate dehydrogenase (LDH), β2 microglobulin, extramedullary involvement, number and location of involvement, AML subtypes, and flow cytometry results were evaluated. Age was associated with CNS involvement at the time of diagnosis in univariate (p = 0.001) and multivariate analyzes (p = 0.006). Extramedullary involvement at diagnosis was related to CNS involvement during follow-up in univariate (p < 0.001) and multivariate analyzes (p = 0.001). Both age and extramedullary involvement were related to CNS involvement at any time in univariate (p = 0.002 and p = 0.001, respectively) and multivariate (p = 0.002 and p = 0.001, respectively) analyzes.

3.4. The prognosis

The median overall survival duration of patients with CNS involvement at diagnosis (5.4 months [0–13.6; 95% confidence interval, CI]) was shorter than those without CNS involvement (16.2 months [10.4–22; 95% CI]) or CNS involvement during follow-up (16.9 months [0–62.4; 95% CI]). No statistical significance was observed (p = 0.5) probably due to the low patient number (Figure).

4. Discussion

In the literature, data about CNS involvement in adult patients with AML is rare. The CNS involvement data generally comes from studies involving pediatric AML.
In our study, CNS involvement in AML was 2.4% at the time of diagnosis, and 4.6% throughout the disease course. Abbot et al. and Felix et al. showed CNS involvement in 29% and 16% of patients at the time of diagnosis in pediatric population, respectively [16,14]. These CNS involvement rates were quite higher than adult population. Del Principe et al. showed CNS involvement with routine CNS evaluation regardless of clinical symptoms in 11% of adult patients at the time of diagnosis [17]. In other studies, CNS involvement rates were between 0.6% and 1.8% in patients with AML at the time of diagnosis. CNS involvement rates were between 2.9% and 5.1% throughout the disease [8,7,18,19]. Del Principe et al. reported that FAB M4-M5 type and high

Table 1. Characteristics of the patient groups.

| CNS involvement                      | At diagnosis (N: 13) | Only during relapse (N: 12) | Anytime (N:25) | Absent (N: 523) | p value |
|--------------------------------------|----------------------|----------------------------|----------------|----------------|---------|
| Sex (F/M)                            | 4/9                  | 6/6                        | 10/15          | 220/303        | 0.61    |
| Age (median, range)                  | 31.4 (18.9–49.5)     | 48.5 (25.6–72.7)           | 40.2 (18.9–72.7)| 51.9 (18.3–88.1)| <0.001  |
| Age (<65 vs older)                   | 13/0                 | 11/1                       | 24/1           | 391/132        | 0.016   |
| ECOG (0–1 vs. 2–4)                   | 7/6                  | 8/4                        | 15/10          | 419/93         | 0.018   |
| De novo/secondary AML                | 13/0                 | 9/3                        | 22/3           | 445/78         | 0.19    |
| AML M4-5 vs other                    | 2/5                  | 4/5                        | 6/10           | 76/221         | 0.44    |
| White blood cell (median, range)     | 10600 (2300–231600)  | 39850 (700–98700)          | 18900 (700–231600)| 7850 (200–321300)| 0.19    |
| White blood cell (>3x10^9/L) (yes/no)| 3/10                 | 6/4                        | 9/14           | 129/335        | 0.075   |
| Lactate dehydrogenase (median, range)| 632 (236–7222)       | 552 (277–2755)             | 619 (236–7222) | 490 (65–8490)  | 0.43    |
| Lactate dehydrogenase (>1000 IU/L)  (yes/no) | 3/6                  | 3/5                        | 6/11           | 71/243         | 0.47    |
| B2-microglobulin (median, range)     | 1950 (1402–2705)     | 1584 (430–1733)            | 1584 (430–2705)| 2243 (818–8372)| 0.12    |
| Other extramedullary involvement     | 7/5                  | 9/2                        | 16/7           | 104/360        | <0.001  |
| ELN* genetic risk group              | 2/3/3                | 3/3/4                      | 5/6/7          | 81/148/55      | 0.35    |
| CBF**-type vs other                  | 1/6                  | 1/7                        | 2/13           | 27/195         | 0.98    |
| APL@ vs others                       | 1/5                  | 1/5                        | 2/10           | 33/153         | 0.99    |
| Duration between diagnosis-CNS       | 0 (0–0.47)           | 8.6 (0.8–49.2)             | 0.46 (0–49.2)  | NA             |         |
| involvement (months)                 |                      |                            |                |                |         |
| Pattern of involvement (LM@@, LM&P#, P, Optic nerve/Eye) | 5, 2, 1, 4 | 6, 1, 4, 1 | 11, 3, 5, 5 | NA | 0.25 |
| Method of diagnosis                  | 8/4                  | 9/3                        | 17/7           | NA             | 0.65    |
| Systemic high-dose* chemotherapy/ intrathecal chemotherapy/ CNS radiotherapy | 7/8/2 | 1/5/1 | 8/13/3 | NA |         |
| Allogeneic stem cell transplant (yes/no)@ | 1/12 | 5/7** | 6/19 | 131/390 | 0.14 |

The sum of the values in the cells may be less than the total number due to missing values *European LeukemiaNet, **core-binding factor, @acute promyelocytic leukemia, @@leptomeningal, #parenchymal, "Higher than 1g/m^2 cytarabine and/or 500 mg/m^2 methotrexate, §before CNS involvement in 4 cases, NA: not applicable.
LDH levels were associated with CNS involvement at the time of diagnosis [17] Cheng et al. showed that high white blood cell counts and inversion 16 were associated with CNS involvement at the time of diagnosis. Alakel et al. showed that complex karyotypes, high LDH levels, FAB M5, and FLT3 mutation were related to CNS involvement.

**Table 2. Univariate and multivariate analyzes for CNS involvement at diagnosis, at relapse and anytime.**

| Risk factors for CNS involvement | Univariate logistic regression* | Multivariate logistic regression** |
|---------------------------------|---------------------------------|----------------------------------|
|                                 | Exp(B) (95% CI) | p value | Exp(B) | p value |
| Age                             | 1.089 (1.037–1.143) | 0.001 | 1.091 (1.025–1.162) | 0.006 |
| Lactate dehydrogenase            | 1 (1–1.001) | 0.075 |                  |        |
| Other extramedullary involvement | 4.48 (1.39–14.4) | 0.012 |                  |        |
| Age                             | 1.044 (1.016–1.073) | 0.002 | 1.049 (1.017–1.082) | 0.002 |
| Other extramedullary involvement | 7.912 (3.170–19.747) | <0.001 | 6.263 (2.428–16.156) | <0.001 |

*Parameters selected for multivariate analysis (p < 0.1) are presented. ** Significant parameters (p < 0.05) are presented. * confidence interval.

**Figure.** Overall survival according to CNS involvement status.
at the time of diagnosis [8]. Rozovsky et al reported that young age, African-American ethnicity and high LDH levels were risk factors for CNS involvement. Holmes et al. [5] and Shihadeh et al. [6] reported a higher incidence of CNS involvement in APL and FAB M4-M5 AML respectively compared to other AML types. Some studies have shown that high white blood cell count, peripheral eosinophilia, high LDH level, male sex, age <50 were risk factors for CNS involvement at the time of diagnosis [20,18,21]. Jabbour et al. showed that age, high LDH level, and FLT 3 mutation were independent risk factors for CNS involvement in multivariate regression model. In our study, younger age was associated with CNS involvement at the time of diagnosis. We found that extramedullary involvement at diagnosis was related to CNS involvement during follow-up. Age and extramedullary involvement were related to CNS involvement at any time. Although CNS involvement at diagnosis was not a prognostic factor in pediatric patients with AML [15,16], it was associated with poor prognosis in adult AML patients [20,22]. Castagnola et al. reported that median overall survival after CNS involvement was 2 months (1–5 months) [2]. Del Principe et al. and Alakel et al. showed that patients with CNS involvement at the time of diagnosis had shorter overall survival [17-8]. In our study, the median overall survival in patients with CNS involvement at the time of diagnosis was shorter than patients who did not experience this complication as similar to the other studies. There was no statistically significant difference between the two groups probably due to low number of patients with CNS disease.

Our study has the advantage of a high total patient number, diagnosed during two decades. We are aware that it has some limitations inherent to retrospective studies, such as some missing data.

5. Conclusion
CNS involvement occurs rarely (4.6%) in AML. Younger age and extramedullary involvement at diagnosis are risk factors for CNS involvement.

Acknowledgment/Disclaimers/Conflict of interest
The author(s) received no financial support for the research, authorship, and/or publication of this art.

The authors declare that they have no conflict of interest.

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