Leukemia Research Reports 20 (2023) 100383

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Characteristics and survival outcomes of patients with atypical chronic myeloid leukemia in the United States: A SEER-based analysis

Dear Editor,

Atypical chronic myeloid leukemia (aCML) is a rare chronic myeloproliferative disease characterized by the absence of the Philadelphia Chromosome (BCR-ABL). It is also known as BCR-ABL negative CML. The clinical and hematologic picture of aCML is like that of BCR-ABL positive chronic myeloid leukemia, but it is more aggressive and carries a worse prognosis. Atypical CML is a disease characterized by neutrophilic leukocytosis and prominent dysgranulopoiesis. Diagnosis of aCML is based on the criteria by The World Health Organization (WHO), which was updated in 2016 [1]. In 2022, the International Consensus Classification of Myeloid Neoplasms and Acute Leukemias developed diagnostic criteria integrating morphologic, clinical, and genomic data [2]. Overall Survival (OS) of 15 months from the largest study thus far [3]. There is no standard treatment for the disease, and outcomes are often poor, even with hematopoietic stem cell transplantation (HSCT) [4,5].

We aim to provide an update on the epidemiology and prognostic factors of aCML in the United States. Due to the rarity of the disease, there is a paucity of population-based studies in the literature that describe the characteristics and survival outcomes in patients with aCML. Such information will contribute to understanding the natural history of the disease and making informed clinical decisions in managing this rare neoplasm.

The Surveillance, Epidemiology, and End Results (SEER) 17 database (2000 – 2020) [6] was utilized in our study. The database contains data from 17 population-based registries in 13 states and covers about 26.5% of the U.S. population, according to the 2020 census. Cases of aCML were identified using the ICD-O-3 code 9876/3. Our search was limited to cases with microscopically confirmed diagnoses of aCML. We extracted data on age at diagnosis, sex, race, year of diagnosis, chemotherapy treatment status, time to treatment, survival time, vital status (dead or alive), and cause of death (whether attributable to aCML or other causes). The study was exempt from institutional review board approval as the database was de-identified.

Statistical analyses were conducted using IBM® SPSS® Statistics version 25. Demographic characteristics were reported in percentages. OS medians were calculated using the Kaplan–Meier method. The Cox proportional hazard regression model was used to determine the prognostic factors of OS. A p-value of <0.05 was considered statistically significant.

We identified 283 cases of atypical CML for the entire study period of 2001 – 2020. The disease was more common in older patients aged >65 years (68.2% vs. 31,8%), men (62.2% vs 37.8%), and Whites (79.5%). Though the absolute

The number of cases of aCML increased from 47 between 2000 and 2005 to 103 between 2016 and 2020 (see Table 1), and the age-adjusted incidence rate remained the same at 0.2 per 1 000 0000 of the population (not shown in Table 1). Chemotherapy was administered to 77.4%

Table 1
Characteristics and survival outcomes of patients with atypical chronic myeloid leukemia.

Age group	n(%)	
<65 years	90 (31.8)	
≥65 years	193 (68.2)	
Gender		
Male	176 (62.2)	
Female	107 (37.8)	
Race		
White	225 (79.5)	
Black	27 (9.5)	
Other*	31 (11)	
Year of Diagnosis		
2001 – 2005	47 (16.6)	
2006 – 2010	49 (17.3)	
2011 – 2015	84 (29.7)	
2016 – 2020	103 (36.4)	
Chemotherapy		
Yes	219 (77.4)	
No/Unknown	64 (22.6)	
Time to treatment in months (n = 217)		
<1	113 (52.1)	
1 – 6	96 (44.2)	
7 – 10	7 (3.2)	
24	1 (0.5)	
Overall Survival	MedianOS: months (95% Confidence Interval)	p
aCML analyzed population**	16.0 (13.8 – 18.2)	0.543
Age group		
<65 years	31.0 (9.8 – 52.2)	<0.001
≥65 years	13.0 (10.6 – 15.4)	
Sex		
Male	17.0 (14.8 – 19.2)	0.543
Female	13.0 (10.4 – 15.6)	
Race		
White	15.0 (13.0 – 17.0)	0.71
Black	18.0 (10.2 – 25.8)	
Other*	16.0 (8.1 – 23.9)	
Year of diagnosis		
2001 – 2005	15.0 (9.6 – 20.4)	0.683
2006 – 2010	13.0 (8.7 – 17.3)	
2011 – 2015	16.0 (12.8 – 19.2)	
2016 - 2020	16.0 (13.1 – 19.0)	
Chemotherapy		
Yes	16.0 (13.7 - 18.3)	0.185
No/Unknown	13.0 (8.6 - 17.4)	

* American Indian/Alaskan Native, Asian/Pacific Islander.
** 5-year survival: 17%.

https://doi.org/10.1016/j.lrr.2023.100383
Received 25 June 2023; Received in revised form 19 July 2023; Accepted 5 August 2023
Available online 6 August 2023

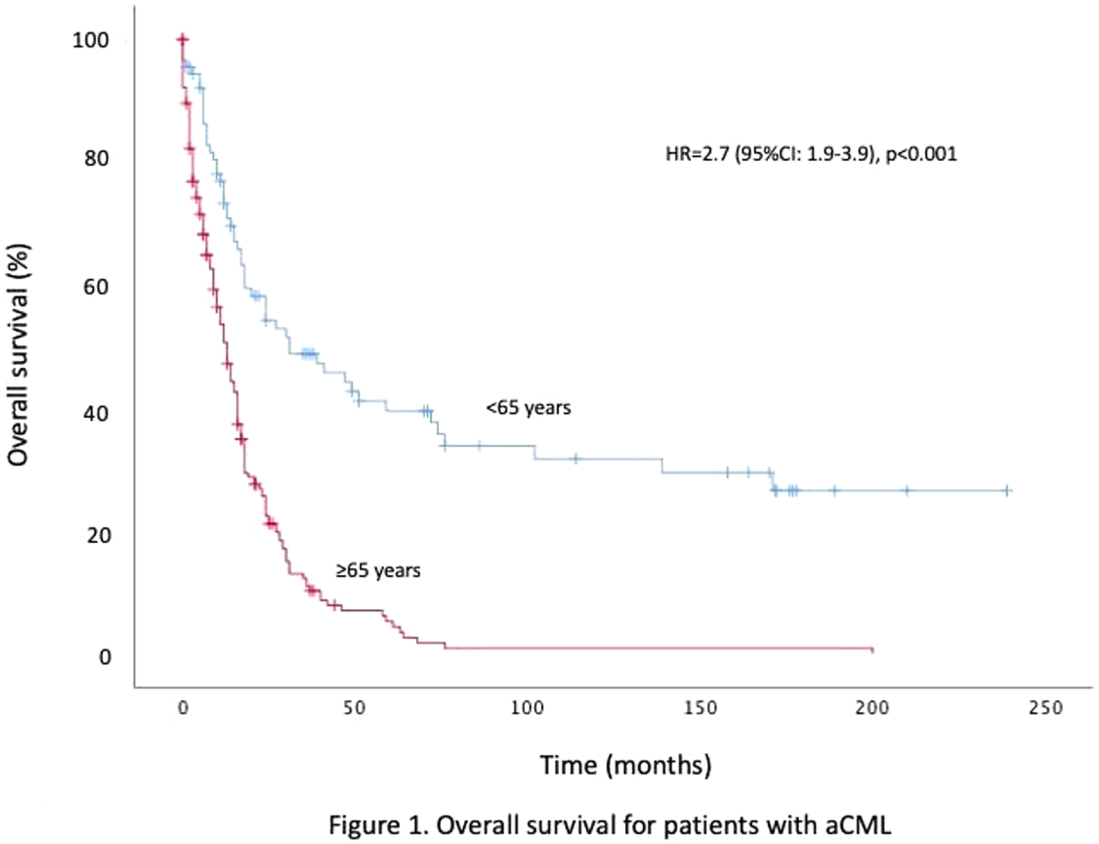

Fig. 1. Overall survival for patients with aCML.

of the patients, with the majority (52.1%) starting treatment during the firstmonth of diagnosis with aCML. The median OS was 16 months (95% CI): 13.8–18.2), and the 5-year OS was 17%. Of the 222 patients that died, mortality was attributed to aCML in 80.6% of cases.

In a univariate analysis, age was the only variable significantly associated with OS, with a median of 13 months (95% CI 10.6 – 15.4) for patients aged 65 years and above, compared to a median of 31 months (95% CI 9.8–52.2) for younger patients ($p < 0.0001$). In the multivariate Cox proportional hazard regression model (accounting for sex, race, year of diagnosis, chemotherapy treatment status, and time to treatment), age ≥65 years (HR 2.7, 95% CI: 1.9 – 3.9, $p < 0.001$) was the only prognostic factor significantly associated with OS (Table 1 and Fig. 1). There was no significant association between race, sex, or year of diagnosis and survival.

Our study's median OS of aCML agrees with that reported in a previous US study [3] but is lower than that reported in a Chinese study, which had a smaller cohort of patients [2]. The independent association of age with OS is supported by a retrospective study by Onida et al. [7], who also found that sex and treatment did not significantly impact OS. Race also does not seem to affect OS, as shown in our study and that of Giri et al. [3]. Most of the patientsdied from the cancer (aCML) itself rather than other causes, further showing the poor prognosis of the disease.

Possible explanations for the continuous increase in the absolute number of cases of aCML over the years include advances in molecular techniques for making the diagnosis and recognition of the disease as a distinct clinical entity by WHO.

Currently, there is no standard treatment available for the management of aCML. Different treatment strategies have been described in the literature, including hydroxyurea, hypomethylating agents, and interferon, often with disappointing results [4,8,9]. HSCT has been regarded as the only potentially curative therapy for eligible patients (significantly younger patients) with aCML [10,11]; however, the results from this treatment modality are mixed, withsome studies reporting dismal outcomes [4,5]. Advances in molecular biology continue to throw more light on the genomic landscape of aCML, and mutations in SETBP1, ASXL1, N/K-RAS, SRSF2, and TET2, and less frequently (< 10%) CBL, CSFR3, JAK2, EZH2, and ETNK1, have been identified [10,11]. In addition, certain genomic rearrangements, such as PDGFβR, a fusion transcript of t(5;10) (q33;q22), have been reported to predict a favorable response to imatinib [12]. In the study, the authors reported clinical and cytogenetic response to imatinib in a patientwith aCML who had the PDGFβR fusion product with a 99% reduction in the transcript expression in peripheral blood [12]. Target therapies such as JAK2 inhibitors and SRC kinase inhibitors have been suggested to have possible therapeutic effects in selected patients with aCML [11,13].

As seen in our study, the lack of improvement in OS over the years (2000 – 2020) calls for more prospective studies evaluating therapeutic modalities that could improve clinical outcomes. There is also the need for policymakers to commit to more support and funding of clinical trials and research aimed at finding effective treatments and improving clinical outcomes for this disease.

The limitations of our study include a lack of information on the molecular features of aCML and the potential for coding errors in the SEER database. However, it undergoes a strict quality assurance process. Also, it would be great to know the time to progress and which chemotherapy was given to the patients, information which is unavailable at this time.

To the best of our knowledge, our study represents the most recent and largest data that describe the frequencies, characteristics, and outcomes of patients with aCML using a population-based data source in the United States - the SEER database. Prospective clinical trials are needed to further explore the molecular features of this rare disease and find effective treatment modalities for improving clinical outcomes.

Declaration of Competing Interest

The authors do not have any interest to declare. The first author (Nosakhare Paul Ilerhunmwuwa) for record purposes is a recipient of the American Society of Hematology Minority Resident Hematology Award with a grant to fund his research on the Predictors of Severe COVID-19 in Sickle Cell Disease.

References

[1] D.A. Arber, A. Orazi, R. Hasserjian, J. Thiele, M.J. Borowitz, M.M. Le Beau, C. D. Bloomfield, M. Cazzola, J.W Vardiman, The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, Blood 127 (20) (2016) 2391–2405, https://doi.org/10.1182/blood-2016-03-643544. May 19Epub 2016 Apr 11. PMID: 27069254.

[2] D.A. Arber, A. Orazi, R.P. Hasserjian, M.J. Borowitz, K.R. Calvo, H.M. Kvasnicka, et al., International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data, Blood 140 (11) (2022) 1200–1228, https://doi.org/10.1182/blood.2022015850. Sep 15PMID: 35767897; PMCID: PMC9479031.

[3] S. Giri, R. Pathak, M.G. Martin, V.R. Bhatt, Characteristics and survival of BCR/ABL negative chronic myeloid leukemia: a retrospective analysis of the surveillance, epidemiology and end results database, Ther. Adv. Hematol. 6 (6) (2015) 308–312, https://doi.org/10.1177/2040620715607416. DecPMID: 26622999; PMCID: PMC4649605.

[4] Y. Sun, Q. Wang, X. Zhang, Z. Zhang, Q. Wang, J. Cen, et al., Molecular genetics and management of world health organization defined atypical chronic myeloid leukemia, Ann. Hematol. 102 (4) (2023) 777–785, https://doi.org/10.1007/s00277-023-05106-8. AprEpub 2023 Feb 3. PMID: 36735076.

[5] P. Mittal, R.M. Saliba, S.A. Giralt, M. Shahjahan, A.I. Cohen, S. Karandish, et al., Allogeneic transplantation: a therapeutic option for myelofibrosis, chronic myelomonocytic leukemia, and Philadelphia-negative/BCR- ABL-negative chronic myelogenous leukemia, Bone Marrow Transplant 33 (10) (2004) 1005–1009, https://doi.org/10.1038/sj.bmt.1704472. MayPMID: 15048141.

[6] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*stat database: incidence - SEER research plus data, 17 registries, Nov 2022 Sub (2000-2020) - linked to county attributes – time-dependent (1990-2021) income/rurality, 1969-2021 counties, National Cancer Institute, DCCPS, surveillance research program, released April 2023, based on the November 2022 submission.

[7] F. Onida, G. Ball, H.M. Kantarjian, T.L. Smith, A. Glassman, M. Albitar, et al., Characteristics and outcome of patients with Philadelphia chromosome-negative, bcr/abl negative chronic myelogenous leukemia, Cancer 95 (8) (2002) 1673–1684, https://doi.org/10.1002/cncr.10832. Oct 15PMID: 12365015.

[8] M. Breccia, F. Biondo, R. Latagliata, I. Carmosino, F. Mandelli, G. Alimena, Identification of risk factors in atypical chronic myeloid leukemia, Haematologica 91 (11) (2006) 1566–1568. NovEpub 2006 Oct 17. PMID: 17043019.

[9] R. Kurzrock, C.E. Bueso-Ramos, H. Kantarjian, E. Freireich, S.L. Tucker, M. Siciliano, et al., BCR rearrangement- negative chronic myelogenous leukemia revisited, J. Clin. Oncol. 19 (11) (2001) 2915–2926, https://doi.org/10.1200/JCO.2001.19.11.2915. Jun 1PMID: 11387365.

[10] E. Crisà, M. Nicolosi, V. Ferri, C. Favini, G. Gaidano, A. Patriarca, Atypical chronic myeloid leukemia: where are we now? Int. J. Mol. Sci. 21 (18) (2020) 6862, https://doi.org/10.3390/ijms21186862. Sep 18PMID: 32962122; PMCID: PMC7555965.

[11] J. Gotlib, J.E. Maxson, T.I. George, J.W. Tyner, The new genetics of chronic neutrophilic leukemia and atypical CML: implications for diagnosis and treatment, Blood 122 (10) (2013) 1707–1711, https://doi.org/10.1182/blood-2013-05-500959. Sep 5Epub 2013 Jul 29. PMID: 23896413; PMCID: PMC3765056.

[12] J.L. Garcia, J. Font de Mora, J.M. Hernandez, J.A. Queizan, N.C. Gutierrez, J. M. Hernandez, J.F San Miguel, Imatinib mesylate elicits a positive clinical response in atypical chronic myeloid leukemia involving the platelet-derived growth factor receptor beta, Blood 102 (7) (2003) 2699–2700, https://doi.org/10.1182/blood-2003- 05-1579. Oct 1PMID: 14504072.

[13] J.E. Maxson, J. Gotlib, D.A. Pollyea, A.G. Fleischman, A. Agarwal, C.A. Eide, D. Bottomly, B. Wilmot, S.K. McWeeney, C.E. Tognon, J.B. Pond, R.H. Collins, B. Goueli, S.T. Oh, M.W. Deininger, B.H. Chang, M.M. Loriaux, B.J. Druker, J. W. Tyner, Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML, N. Engl. J. Med. 368 (19) (2013) 1781–1790, https://doi.org/10.1056/NEJMoa1214514. May 9PMID: 23656643; PMCID: PMC3730275.

Nosakhare Paul Ilerhunmwuwa[a,*], Mustafa Wasifuddin[a], Henry Becerra[b], Aditya Keerthi Rayapureddy[c], Jen Chin Wang[d]

[a] *Department of Internal Medicine, One Brooklyn Health/Brookdale University Hospital and Medical Center, Brooklyn, New York, United States of America*

[b] *Incoming resident, Department of Internal Medicine, One Brooklyn Health/Brookdale University Hospital and Medical Center, Brooklyn, New York, United States of America*

[c] *Department of Internal Medicine, One Brooklyn Health/Interfaith Medical Center, Brooklyn, New York, United States of America*

[d] *Department of Hematology and Oncology, One Brooklyn Health/Brookdale University Hospital and Medical Center, Brooklyn, New York, United States of America*

[*] Corresponding author.
E-mail address: ilerhunmwuwa@gmail.com (N.P. Ilerhunmwuwa).