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Survival of patients with mixed phenotype acute leukemias: A large population-based study

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ABSTRACT

Little is known about the incidence and treatment outcome of patients with acute biphenotypic leukemias. The World Health Organization (WHO) established the term of acute leukemia of ambiguous phenotype in 2001 (revised in 2008) introducing the term of mixed phenotype acute leukemias. Using the database of the Surveillance, Epidemiology, and End Results registry (SEER), we identified 313 patients with mixed phenotype acute leukemias and compared them with 14,739 patients with acute lymphoblastic leukemia and 34,326 patients with acute myelogenous leukemias diagnosed between 2001 and 2011. As a further control group, 1777 patients were included who were not classified as myeloid, lymphoid or biphenotypic (other acute leukemias). The incidence of mixed phenotype acute leukemias is 0.35 cases/1,000,000 person-years. In a multivariate analysis, the prognosis depends strongly on age (as with other leukemias) and it has the worst outcome of all four types of leukemia. However, the prognosis has improved, comparing 2001–2005 with 2006–2011. We present the first comprehensive, population-based study of acute biphenotypic or mixed phenotype acute leukemias according to the WHO classification. Especially in older patients, the prognosis is unfavorable and new treatments should be investigated.

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1. Introduction

The treatment of acute leukemias has made significant advances over the last three decades [1,2]. The treatment approach has changed from palliative in many cases to curative. Examples are acute lymphoblastic leukemias in the pediatric and young adult age group, and acute promyelocytic and core-binding factor leukemias for adults. The use of tyrosine kinase inhibitors has improved the prognosis of acute lymphoblastic leukemias expressing the Philadelphia chromosome. Part of the progress in acute leukemias is due to the early use of allogeneic transplantation. With more sophisticated diagnosis, the treatment can be individualized according to each patient's risk [3]. In this context, the prognosis of acute biphenotypic leukemias (bearing both lymphoid and myeloid markers) is not well described. Acute biphenotypic leukemias (ABiL) are rare (2–5% of all acute leukemias) [4,5]. Originally, ABiL (or mixed lineage acute leukemias) were defined by the European Group for the Immunological Classification of Leukemias. Later, the WHO classification and definitions were universally accepted [4,6] (see Table 1 for definitions). Until now, only smaller case series of mixed phenotype acute leukemias (MPAL) were published [7–12,14–18]. In the present study we investigated the incidence and outcome of MPAL and compared these with acute lymphoid, acute myeloid and other not well characterized acute leukemias in a large database.

2. Methods

We used data obtained from the registries participating in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry that covers 27% of the population in the United States [13]. SEER includes 18 population-based registries and is a standard for cancer epidemiology in the United States. The SEER registry was last accessed on 11/15/2014. The diagnosis of acute leukemia was based on the SEER standard cytomorphological criteria. The SEER 18 Regions Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2013 Sub (1973–2011 varying) were used to select patients while the Primary Site of 421 or the Site and Morphology Site recode ICD-O-3/WHO 2008 = 'Leukemia' were used. The year of diagnosis was limited to 2001 or later. All cases (n = 52,449) including leukemias with a preceding different malignancy were included to select for the patients. Patients with missing survival time (n = 1344) were excluded from this study. The final analysis in this study has 51,155 patients.

Patients were grouped to AML (acute myeloid leukemia, acute monocytic leukemia, n = 34,326), ALL (acute lymphocytic leukemia, n = 14,739), and other acute leukemia.

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Table 1
Definition of acute leukemias of ambiguous lineage (MPAL) according to the 2008 WHO classification [6].

Myeloid lineage	Myeloperoxidase or monocytic differentiation (at least 2 of the following markers: NSE, CD11c, CD14, CD64, lysozyme)
T lineage	Cytoplasmic CD3 or surface CD3
B lineage	Strong CD19 and strong expression of at least one of the following: CD79a, cy CD22, CD10 or weak CD19 and strong expression of at least 2 of the following: CD79, cy CD22, CD10

A sub-category among other acute leukemias were defined as MPAL/ABiL and these included the following ICD-O-3 Morphology code:

9805/3 Acute biphenotypic leukemia
9806/3 Mixed phenotype acute leukemia with t(9;22)(q34;q11.2);BCR-ABL1
9807/3 Mixed phenotype acute leukemia with t(v;11q23);MLL rearranged
9808/3 Mixed phenotype acute leukemia, B/myeloid, NOS
9809/3 Mixed phenotype acute leukemia, T/myeloid, NOS.

The category of "other acute leukemias" was designated as OAL after subtracting cases of ABiL (Histologic_Type_ICD_O_3 of 9801 to 9931, $n = 1777$). The incidence of leukemia of patients was calculated by using SEERStat 8.1.5 (data from SEER Region 18).

The cause of death due to leukemia was used for the cause-specific survival analysis. Survival time (months) was calculated between the date of death (or date of last contact) and date of diagnosis. Details of definition for survival can be found in the http://seer.cancer.gov/survivaltime. In the current manuscript, for simplicity, the overall survival or survival are used to refer to the cause specific survival.

The Kaplan–Meier Method/Product-limit was used to estimate the survival and Logrank test was used to compare the difference of survival between factors. Multivariate Cox regression was used to estimate the effect of factors on survival. The direct adjusted survival plot were also derived from multivariate Cox regression. A multiple comparison adjustment was made when appropriate. All p-values <0.05 were considered statistically significant. Statistical software SAS 9.4 for Windows was used for all data management and statistical analysis and modeling.

3. Results

The incidence of MPAL is shown in Table 2 and compared with ALL, AML and OAL (mostly undifferentiated or unclassifiable leukemias). MPAL has the lowest incidence rate as compared to other three types.

Overall, MPAL are rare and have an annual incidence of 0.35 cases per 1,000,000 person-years. The incidence is higher in male versus female (0.45 vs. 0.26/10^6). The incidence of MPAL has bimodal age distribution. Two age peaks are observed (19 years and younger and 60 years and older). The incidence is not statistically different among ethnic groups and periods between 2001–2005 and 2006–2011.

The age distribution of all four types of leukemia is shown in Table 3. Patients with MPAL are younger (median age = 50) than patients with AML and older than patients with ALL. Patients with "other acute leukemias" are even older than patients with AML.

The demographic characteristics of all four types of leukemias are shown in Table 4 and these final data were used for the survival analysis. MPAL make up only 0.614% of all leukemias with 313 cases in which 60.7% are male and 39.3% are female.

In a univariate analysis, the survival of all types of acute leukemias is shown in Fig. 1. It has strong age dependence (young patients having the best survival). Fig. 2 depicts the survival of the four types of leukemia studied. The survival of MPAL is highly different from (worse than) ALL and is statistically closer to AML and OAL. Fig. 3B shows that the survival of patients diagnosed with MPAL has improved when the time period of 2006–2011 (median OS > 5.8 years) was compared with 2001–2005 (median OS ≈ 1 year).

Figs. 4–7 show the overall survival for ALL, AML, OAL and MPAL according to the age categories 0–19 years, 20–30 years, 40–59 years, and 60 years and older in the univariate analysis (part A) and directed adjusted survival (part B), respectively. In part A of these figures the unadjusted survival by age group are shown; direct adjusted survival is shown in part B (adjusted factors included gender, race, ethnicity and year of diagnosis). When the prognosis of MPAL was stratified by age group, and survival outcomes were compared with the other types of leukemia, the worse prognosis persisted regardless of age (data not shown).

A multivariate Cox regression was performed for all four types of leukemia combined and is shown in the left part of Table 5. Adjusting for other factors, the prognosis of acute leukemia depends on age with younger patients having the best prognosis. Overall, Black or Hispanic ethnicity and female sex predicted a worse outcome in the entire group of acute leukemias. When MPAL was compared with ALL and AML, it had the worst outcome in the multivariate analysis with the risk of death increased by 59%, and 26% respectively. The risk of death was similar between MPAL and OAL.

This is in part confirmed for the subgroup survival analysis of MPAL (African American ethnicity) which is presented in the right part of Table 5. The multivariate analysis confirmed that the prognosis of acute leukemias improved in recent years (26% improvement of survival for patients diagnosed after 2005,

Table 2
Age-adjusted incidence rate of ALL, AML, OAL and MPAL according to race/ethnicity and age, SEER-18, 2001–2011.

		ALL		AML		OAL		MPAL	
		N	Rate	*N*	Rate	*N*	Rate	*N*	Rate
	All	14,843	16.36	35,196	39.54	2144	2.44	316	0.35
Age	0–19	8866	34.32	2163	8.29	97	0.37	81	0.31
	20–39	1938	7.45#	3250	12.75#	103	0.4	40	0.15#
	40–59	1969	7.77#	7755	30.06#	247	0.96#	74	0.29
	60–74	2070	14.25#	22,028	154.90#	1697	11.92#	121	0.84#
Gender	Male	8353	18.52	19,062	48.59	1105	3.04	192	0.45
	Female	6490	14.25#	16,134	33.02#	1039	2.02#	124	0.26#
Race	White	12,478	18.15	29,484	41.08	1812	2.5	252	0.36
	Black	1105	9.36#	2954	33.10#	209	2.58	34	0.33
	Other	1260	12.86#	2758	32.12#	123	1.58#	30	0.32
Ethnicity	Non-Hispanic	9847	14.33	31,097	40.09	1927	2.46	256	0.34
	Hispanic	4996	23.52#	4099	33.71#	217	2.15	60	0.38
Period	2001–2005	6405	15.89	14,992	39.01	1117	2.97	137	0.35
	2006–2011	8438	16.74#	20,204	39.99#	1027	2.04#	179	0.35

Rate: Frequency/10^6 person-years.
Statistically different from reference category ($p < 0.05$).