Leukemia Research 71 (2018) 95–99

Contents lists available at ScienceDirect

Leukemia Research

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

Research paper

Incidence and survival of therapy related myeloid neoplasm in United States

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ARTICLE INFO

Keywords:
Leukemia
Myelodysplasia
Survival
Incidence
SEER
Therapy

ABSTRACT

Background: Therapy related myeloid neoplasm (t-MN) is an emerging challenge in the current era. However, real world data on its incidence and survival at the population level remains sparse.
Methods: Using Surveillance Epidemiology and End Results (SEER-18) database, we identified patients aged ≥20 years with pathologically confirmed t-MN diagnosed between the years 2001–2014 and actively followed. Incidence rate per 100,000 population and incidence rate ratio (IRR) were calculated. Overall survival (OS) was calculated by Kaplan-Meier method with determinants analyzed by Cox proportional hazard regression method.
Results: A total of 1093 patients with a median age of 65 years were identified. Overall incidence of t-MN was 0.13 cases/100,000 population and showed significant variations with age, race and the period of diagnosis. Two year OS significantly declined with increasing age (51.3% in age group 20–39, 33.9% in age group 40–59, 19.3% in age group 60–79 and 0% in age ≥ 80, $p < 0.01$). OS has improved over period (year 2001–2007 − 22.1% vs. year 2008–2014 −26.9%, $p = 0.01$). On multivariate analysis, increasing age was associated with significantly higher mortality. Compared to the period 2001–2007, a significantly lower risk for mortality was seen in the period 2008–2014 (HR 0.73, CI 0.58–0.92, $p < 0.01$).
Conclusions: Incidence of t-MN has significantly increased in the last decade. Although OS at the population level is improving over time, outcomes of this disorder continue to remain poor, highlighting the need for novel therapies.

1. Introduction

Therapy related myeloid neoplasm (t-MN) is an emerging challenge in the current era given that newer therapies are improving the life expectancy of patients diagnosed with cancer. This condition arises as a result of exposure to prior chemotherapy or radiotherapy used to treat malignant or non-malignant conditions. The World Health Organization (WHO) 2001 classification of tumors of hematopoietic and lymphoid tissues had initially described this disorder with two subtypes – therapy related acute myeloid leukemia (t-AML) and therapy related myelodysplastic syndrome (t-MDS) [1]. Both these subtypes have common clinical features, treatment strategies and very poor prognosis. Hence, the 2008 WHO classification merged these two subtypes under one entity labeled as therapy related myeloid neoplasm [2]. Over the last few years, several studies have tried to address the pathogenesis of this disorder; however, the exact mechanism by which it arises is still unknown. Exposure to chemotherapeutic agents such as alkylators or topoisomerase inhibitors was initially thought to induce DNA damage resulting in adverse chromosomal alterations and genetic mutations such as TP53 mutations [3–5]. Recent studies have shown alternative possibilities for the disease mechanism such as the presence of clonal hematopoiesis of indeterminate potential (CHIP) in patients with t-MN even prior to exposure to any chemotherapy, suggesting existence of non-therapy related risk factors that predispose patients to t-MN development [6,7]. Additionally, studies have also suggested that there is a selective expansion of preexisting clones such as TP53 after exposure to cytotoxic chemotherapy [8].

Prognosis of t-MN has generally remained dismal with overall survival (OS) ranging from 8 to 10 months [9,10]. The reason for this poor prognosis includes biological resistance to treatment, aggressive nature of the disease, adverse cytogenetic features, older age at diagnosis, comorbid conditions, poor bone marrow reserve from prior chemotherapy leading to inability in tolerating intensive treatments. In the recent era, treatment strategies such as multiagent chemotherapy, hypomethylating agents and allogeneic hematopoietic cell transplantation are available to manage these patients along with better supportive care. Although prior studies have described the outcomes of this disorder, population level data on the incidence and survival of this

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https://doi.org/10.1016/j.leukres.2018.07.013
Received 5 May 2018; Received in revised form 12 July 2018; Accepted 13 July 2018

disorder in US remains sparse. In this study, we have utilized the surveillance epidemiology end results (SEER) database to explore the outcomes following the diagnosis of t-MN.

2. Methods

We performed a retrospective analysis of the SEER database, a U.S. population-based registry maintained by the National Cancer Institute. Patients with t-MN were identified using International Classification of Diseases for Oncology (ICD-0-3) code (9920/3) from the SEER-18 registry (November 2016 submission data) [11]. The study period included the years 2001 through 2014. SEER-18 registry includes the following sites: Alaska, Arizona, Atlanta (Georgia), Connecticut, Detroit (Michigan), Hawaii, Iowa, New Mexico, Rural Georgia, San Francisco – Oakland (California), San Jose – Monterey (California), Seattle (Washington), Utah, Kentucky, Los Angeles, Louisiana, New Jersey, Greater Georgia and covers approximately 27.8% of the U.S. population. The database provides information about patient demographics, initial treatment (annotated as chemotherapy "yes" or "no/unknown"), and survival duration. However, the data on patient symptoms, performance status, prognostic factors, treatments such as specific chemotherapeutic agents used and hematopoietic cell transplantation are not provided.

Inclusion criteria for the study were age 20 years and above at diagnosis, histologically confirmed t-MN, diagnosis between the years 2001–2014, known race and being on active follow-up. After obtaining the data, race was classified as Whites, Blacks, and other races (Asian/Pacific Islander and American Indians). Age at diagnosis was stratified into 4 groups (20–39, 40–59, 60–79, 80 years and above). Period of diagnosis was divided into two groups – 2001–2007 and 2008–2014, in order to divide them equally. The study did not involve any direct interaction with human subjects and was exempted by the institutional review board.

3. Statistical methods

Baseline demographic characteristics of the study groups were described using descriptive statistics with median (for age) and proportions for categorical variables. Age adjusted incidence rate per 100,000 population and the incidence rate ratio (IRR) were calculated using SEER stat software with the year 2000 US population as the reference standard. For incidence analysis, all cases who met the study criteria were included. Survival analysis was performed using Kaplan-Meier method and compared using log-rank test. In order to identify the impact of available treatment options over time, only patients who received treatment were included for survival analysis. Sample size < 10 was not identified separately according to data requirement. OS (in months) was calculated from the time of diagnosis to death from any cause, and patients were censored if they were reported to be alive at the last follow-up or at the end of the study period. Median OS and 2-year OS for each group were described. Factors influencing OS were analyzed using Cox-proportional hazard regression method after assessing and satisfying proportional hazard assumption. All statistical analyses were conducted with a two sided significant p value of < 0.05. Statistical analyses were performed using SEER stat software and SPSS version 22.

4. Results

4.1. Baseline characteristics

A total of 1093 patients with t-MN who met the study criteria were identified. Median age of the study population was 65 years (range 20–97). Majority of the patients were over the age 60 (64.7%), females (55.5%), Whites (88.1%) and had 1014 prior malignancy related information available. Chemotherapy status (recorded as received) was

Table 1
Baseline characteristics.

Parameter	Number
Age (years)	
20-39	68 (6.2%)
40-59	317 (29%)
60-79	606 (55.4%)
≥ 80	102 (9.3%)
Gender	
Male	486 (44.5%)
Female	607 (55.5%)
Race	
White	963 (88.1%)
Black	69 (6.3%)
Other	61 (5.6%)
Period	
2001-2007	167 (15.3%)
2008-2014	926 (84.7%)
Chemotherapy	
Yes	750 (68.6%)
No/unknown	343 (31.4%)
Chemotherapy status by period	
2001-2007	
Yes	122 (73%)
No/Unknown	45 (27%)
2008-2014	
Yes	628 (67.8%)
No/Unknown	298 (32.2%)
Prior malignancy	
Acute lymphoblastic leukemia	36 (3.6%)
GI	53 (5.2%)
Sarcoma and bone tumors	43 (4.3%)
Brain	14 (1.4%)
Ovary	45 (4.4%)
Uterus	35 (3.5%)
Chronic lymphocytic leukemia	31 (3%)
Breast	208 (20.6%)
Head/neck	18 (1.8%)
Hodgkin lymphoma	30 (2.9%)
Non-hodgkin lymphoma	258 (25.6%)
Kidney	12 (1.1%)
Bladder	18 (1.8%)
Prostate	43 (4.2%)
Lung	60 (5.9%)
Melanoma	25 (2.4%)
Myeloma/plasma cell dyscrasia	52 (5.2%)
Thyroid	10 (0.9%)
Others	23 (2.2%)
SEER registry	
Atlanta	40 (3.7%)
California	190 (17.4%)
Connecticut	48 (4.4%)
Detroit	63 (5.8%)
Greater Georgia	87 (8.0%)
Hawaii	15 (1.4%)
Iowa	85 (7.8%)
Kentucky	76 (7.0%)
Los Angeles	85 (7.8%)
Louisiana	39 (3.6%)
New Jersey	99 (9.1%)
New Mexico	20 (1.8%)
San Francisco	77 (7%)
San Jose	25 (2.3%)
Seattle	91 (8.3%)
Utah	47 (4.3%)

GI – Gastrointestinal including colorectal, stomach, pancreas, esophageal, hepatobiliary and anal cancers; Others – include adrenal, eye/orbital, chronic myeloid leukemia, kaposi's sarcoma, testis, vulva, neuroendocrine tumors and cervical cancer.