LETTERS TO THE EDITOR

Prevalence and characteristics of survivors from acute myeloid leukemia in Sweden

Leukemia (2017) 31, 728–731; doi:10.1038/leu.2016.312

The incidence of acute myeloid leukemia (AML) is documented from national cancer registries,1,2 with limited information on specific subtypes, and the crude prevalence is known for some countries.3,4 However, the characteristics of the prevalent population are unknown. We therefore used Swedish registries to identify and characterize Swedish citizens surviving on 1 January 2014 after an AML diagnosis made during 1997–2013 (n = 1337). They constituted 20% of a total of 6581 AML patients in the Swedish AML and NOPHO (Nordic Society of Pediatric Haematology and Oncology) Registries. The median age of survivors was 51 years at diagnosis and they were aged 59 years in 2014. The overall prevalence was 13.7 per 100 000. Seventeen percent had had acute promyelocytic leukemia (APL) or core binding factor (CBF) leukemia, and 441 (33%) had undergone allogeneic stem cell transplantation (alloSCT). Most long-term survivors had normal karyotype, but some had genetic abnormalities, including high-risk features. Long-term survivors are heterogeneous, including older people and those with intermediate/high-risk genetics, and most did not have alloSCT.

The Swedish AML registry has collected extensive data from almost all (98%) adult AML cases in Swedish citizens diagnosed since 1997, and survival follow-up is updated daily and complete. In this report, patients with pediatric AML diagnosed in 1997–2013 were added from the complete Swedish part of the NOPHO database. This thus permits a comprehensive analysis of the current prevalent population following a diagnosis of AML since 1997. Data including updated survival were extracted in April 2015, and we chose to analyze the prevalence on 1 January 2014, to ensure adequate reporting. Genetic results, including molecular data (FLT3-ITD, NPM1 mutation), were prospectively reported from 2007, whereas karyotype, but no molecular data, was retrospectively retrieved from patients diagnosed in 1997–2006, as previously reported.5 CEBPA mutations were only reported since 2012, and were therefore not analyzed. Standard descriptive statistical analysis using Statistica 12 software (Tulsa, OK) was performed.

At data extraction the registry contained files on 6289 adult patients and 292 pediatric patients diagnosed since 1 January 1997, all with complete survival update, except for nine emigrants. On 1 January 2014 there were 1337 people surviving (20.3%) following an AML diagnosis, of which 661 were males (49%) and 676 females. Characteristics of the surviving patients are given in Table 1. There were 217 living patients diagnosed in 2013, and 244 diagnosed in 2011–2012, and thus 876 (66%) had survived 3 years or more, including 344 (26%) who had survived 10 years or more.

The overall prevalence was 13.7 per 100 000 inhabitants (males 13.2 and females 13.9 per 100 000), which is similar to the reported corresponding prevalence of AML in the other Nordic countries as on 31 December 2012 (range 12.2–16.8 per 100 000).4 Incidence and prevalence by sex and 5-year age cohorts are shown in Figures 1a and b.

Cancer patients recently diagnosed often have ongoing treatment, with higher relapse rates and death rates than long-term survivors. It is thus useful to analyze partial prevalence, that is, patients diagnosed during a fixed time in the past, as done in the NORDCAN project.4 In this study the 1-year prevalence was 2.2/100 000 (other Nordic countries, range 1.2–2.3), and the 3-, 5- and 10-year prevalence was 4.7, 6.8 and 10.2/100 000, respectively (other Nordic countries: ranges 2.7–4.8, 3.7–6.4 and 6.4–9.7, respectively).

In order to show the primary characteristics of an AML population with a good chance of long-term cure, we separately analyzed patients surviving for more than 3 years, that is, diagnosed in 1997–2010, for which the prevalence was 9.0 per 100 000 (Table 1). Among the long-term survivors there were 101 patients with APL, of which one had had alloSCT after relapse. AlloSCT for non-APL AML was reported for 331 patients diagnosed during 1997–2010, and 444 non-APL patients were long-term survivors without alloSCT. As expected, alloSCT patients were younger, and the median age among recently diagnosed patients was higher.

AML remains a devastating disease, with poor long-term outcome. Only one-fifth of patients diagnosed with AML during the 17-year period 1997–2013 were alive on 1 January 2014, and one-third of them had been diagnosed within the past 3 years. As expected, the age distribution of prevalent patients was skewed 15 years towards younger individuals, and there was an accumulation of APL and a depletion of patients with high-risk karyotypes as compared to the incident population6 (Table 1). However, perhaps surprisingly, the prevalence exceeded the incidence up to age 85, and only 38% of the long-term survivors had received alloSCT. Subsequently, there were people surviving long-term without alloSCT despite complex and other high-risk karyotypes, and one quarter of non-transplanted long-term survivors were aged 70 and over. Less than one in four of the long-term survivors had had APL, CBF leukemia or normal karyotype with NPM1 mutation/FLT3 wild type. Thus, our predictive markers are not always accurate. Consequently, we need to further develop both therapies and our ability to predict the outcome, and in most cases not refrain from treating even patients with poor risk features.

This study emerges from a long-standing nation-wide patient registry. The comparison to the compulsory Swedish Cancer registry shows an almost complete coverage due to extensive monitoring and requests for missing data. Individual data are reported by hematologists in charge. The survival update is complete, except for a few emigrants. Importantly, our data contain solid diagnostic information, such as morphological and genetic subtype, and information if alloSCT was performed; however, we believe that there may be some underreporting of recent transplants.

However, our data are somewhat incomplete. It does not contain long-term survivors diagnosed before 1997. We could estimate that there should be a few hundred more such patients. However, our prevalence is similar to the total prevalence reported from the other Nordic countries in the NORDCAN project.4
Furthermore, we lack information about FLT3 and NPM1 abnormalities in patients diagnosed before 2007, and we lack reports on CEBPA. In Table 1 we show the characteristics of the incident population during the period 2006-2013; however, there was still underreporting of molecular abnormalities during this period. Thus, we should expect that a significant proportion of patients with normal karyotype had favorable risk from NPM1mut/FLT3wt or CEBPA double mutation. Furthermore, 9% of the overall prevalent population and 12% of the long-term survivors had uncharacterized karyotype; this is not exceptional. Karyotype was more often missing in the incident population, since sampling was not mandatory in patients not eligible for therapy.

We believe that the main information from this study is the confirmation that AML is a very heterogeneous disease even within our currently established and validated risk groups. Also, survivors constitute a heterogeneous mix of patients, with a wide range of ages, with different genetic risk, and many did not have a

Figure 1. (a) Incidence of AML per 100 000 inhabitants during 1997 – 2013 by age; (b) prevalence as on 1 January 2014 of AML per 100 000 inhabitants by age; and (c) prevalence as on 1 January 2014 of AML diagnosed during 1997 – 2010 per 100 000 inhabitants by age.
We thank the data managers at Regional Cancer Center South for running the Swedish Adult AML registry, and the NOPHO leukemia database. The study was approved from the Swedish Cancer Society.

ACKNOWLEDGEMENTS

We thank the data managers at Regional Cancer Center South for running the Swedish Adult AML registry, and the NOPHO leukemia database. The study was supported from the Swedish Cancer Society.

PREVIOUS ALLOSCT. We thus need newer and better therapies, but should still aim to treat also older and high-risk patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

GJ planned the study, did the analyses, and wrote the manuscript. JA provided data on pediatric patients. All authors contributed to the maintenance and reporting of data to the AML registries, critically reviewed the data and approved the manuscript.

Letters to the Editor

Table 1. Characteristics of prevalent patients in January 2014 by sex and year of AML diagnosis, with laboratory values at diagnosis, median and quartile ranges given.

|                | Diagnosis 2011–2013 | Diagnosis 1997–2010 | All prevalent Patients | All incident Patients |
|----------------|----------------------|----------------------|------------------------|-----------------------|
|                | AlloSCT | No alloSCT | APL | All prevalent Patients | Diagnosis 2006–2013 |
| Number         | 461 (34.5%) | 331 (24.8%) | 444 (33.2%) | 101 (7.6%) | 1337 | 3090 |
| **Age at diagnosis, years** | | | | | | |
| M              | 59 (41–70) | 44 (28–54) | 52 (17–62) | 53 (39–61) | 52 (32–64) | 69 (57–78) |
| F              | 64 (44–73) | 46 (33–54) | 50 (15–63) | 39 (26–50) | 51 (33–64) | 71 (58–80) |
| **Age 2014, years** | | | | | | |
| M              | 51 (43–71) | 54 (38–64) | 60 (27–69) | 63 (48–69) | 59 (39–68) | |
| F              | 65 (45–74) | 55 (42–64) | 60 (27–72) | 49 (35–61) | 59 (40–69) | |
| **Hemoglobin, g/l** | | | | | | |
| M              | 97 (85–112) | 96 (82–107) | 100 (89–113) | 97 (85–110) | 94 (85–112) | 94 (83–107) |
| F              | 95 (84–108) | 94 (84–105) | 94 (81–110) | 102 (96–122) | 95 (84–108) | 95 (84–105) |
| **WBC, x10^9/l** | | | | | | |
| M              | 8.2 (2.2–32.4) | 5.5 (1.8–47) | 9.2 (3.4–38) | 1.8 (0.7–6.7) | 8.1 (2.2–36) | 9.3 (2.3–38) |
| F              | 6.1 (1.8–28.3) | 11.8 (3.2–54) | 10 (3.7–45.2) | 1.7 (1.1–6.7) | 8.3 (2.2–33) | 9.9 (2.4–45) |
| **Platelets, x10^9/l** | | | | | | |
| M              | 67 (36–120.5) | 73 (31–137) | 62 (35–131) | 32 (17–55) | 65 (34–119) | 55 (30–107) |
| F              | 76 (33–133) | 82 (36–148) | 61 (44–106) | 41 (29–74) | 71 (35–129) | 64 (32–126) |
| **BM blasts, %** | | | | | | |
| M              | 51 (30–75) | 53 (27–75) | 46 (30–75) | 26 (19–74) | 50 (27–75) | |
| F              | 50 (30–72.5) | 52 (30–80) | 63 (35–78) | 50 (10–81) | 52 (30–75) | |
| **Observation time, years** | | | | | | |
| M              | 1.2 (0.5–2.0) | 8.3 (4.9–12.9) | 7.6 (4.8–11.7) | 7.5 (5.7–12.1) | 4.4 (1.7–9.0) | |
| F              | 1.0 (0.4–1.7) | 8.1 (5.4–11.7) | 9.1 (5.7–12.3) | 10.0 (5.5–12.9) | 5.9 (2.0–10.9) | |

Abbreviations: APL, acute promyelocytic leukemia; BM, bone marrow; F, female; M, male; SCT, stem cell transplantation; WBC, white blood cells. Lab values were available only for patients diagnosed from 2007. For long-term survivors, that is, those diagnosed during 1997–2010, patients with APL are reported separately and the remaining patients are reported depending on whether allogeneic stem cell transplantation had been performed. For comparison, data from the incident patients diagnosed during 2006–2013 are shown. Karyotype was classified hierarchically from top to bottom, so patients are only listed once.
Plastic CD34 and CD38 expression in adult B–cell precursor acute lymphoblastic leukemia explains ambiguity of leukemia-initiating stem cell populations

Leukemia (2017) 31, 731–734; doi:10.1038/leu.2016.315

B-cell precursor acute lymphoblastic leukemia (BCP-ALL) is an aggressive hematologic malignancy of bone-marrow (BM)-derived lymphoid precursor cells at various stages of differentiation.\(^1\) Although first-line therapy with chemotherapy and—in the case of BCR-ABL1 positive ALL—tyrosine kinase inhibitors is initially highly effective with remission rates of \(>90\)%, the overall survival rate in adult patients is 40–50% across all risk groups.\(^2\)–\(^3\) Relapse originates from putative leukemia-initiating cells (LICs) that are intrinsically resistant to chemotherapeutic regimens, which may explain the poor long-term prognosis of patients with disease recurrence. Eradication of LICs thus is a principal aim of novel therapeutic approaches. A prerequisite for developing effective LIC-targeted treatments is the ability to identify and clinically monitor LICs in ALL, a goal that has to date been elusive. The existence, phenotype, biological properties and the hierarchical organization of LICs in BCP-ALL remain highly controversial.\(^4\)

The prospective enrichment of LICs in ALL using the surface markers CD34 and CD38 (also in combination with other markers) —as well-established in acute myelogenous leukemia —largely failed, resulting in highly variable results.\(^5\)–\(^8\) We investigated the reason for these ambiguous results by observing the expression of these markers even at single cell level in high temporal resolution.

We found that CD34 and CD38 are highly plastic on individual BCP-ALL cells and are up- or downregulated in one cell generation within hours, and may not be useful for prospective LIC isolation. To investigate the plasticity of CD34 and CD38 surface marker expression in BCP-ALL, we utilized a unique ALL patient-derived long-term cell culture system (PDLTCs) established from patient PH.\(^9\) The PDLTC-PH reflects the polyclonal propensity of the disease and remains genetically and functionally stable in culture for more than 6 months (Nijmeijer et al., 2014; data not shown). Furthermore, we achieved to generate isogenic clonal PDLTC-PH subcultures, which are invaluable to investigate relations between phenotypes and distinct function.

First, we confirmed the presence of cells with LIC activity in PDLTC-PH by injecting \(5 \times 10^6\) unsorted bulk cells intravenously into sublethally-irradiated immune-compromised NSG mice, revealing human ALL cell engraftment and leukemia progression in the peripheral blood (PB) of the recipients via FACS as well as their survival (Figure 1a, Supplementary Methods). After 62 days, we found the first ALL cells in the PB, and the human ALL cell clonality successively increased over time until the mice died of the disease after 119 days in average (±4.6 days), with a high proportion of ALL cells in the BM (Figure 1a). After confirming the existence of LICs in PDLTC-PH, we checked for the cell surface expression of CD34 (APC clone 8G12, BD, Heidelberg, Germany) and CD38 (PE clone HB7 eBioscience, Frankfurt, Germany) in these PDLTCs via FACS (FACS Canto, BD). These are indicative surface markers to determine normal hematopoietic stem and progenitor populations, and LIC-enriched fractions in acute myelogenous leukemia explains ambiguity of LICs in BCP-ALL, a goal that has to date been elusive. The existence, phenotype, biological properties and the hierarchical organization of LICs in BCP-ALL remain highly controversial.\(^4\)