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Keywords: Chronic myelomonocytic leukemia, incidence rate, relative and observed survival, population-based cancer registry

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Abstract: Chronic myelomonocytic leukemia is a very rare blood cancer observed mostly in the elderly. Here we report the incidence trends and survival of patients with chronic myelomonocytic leukemia over a 15-year period (1993-2007). Cases were provided by the population-based Girona Cancer Registry. The crude incidence rate was 0.72/100,000 inhabitants/year. No statistically significant increase in trends was detected over the 15 years. Median overall survival was 28 months although survival markedly decreased with advancing age. The 5-years observed and relative survival were 20% and 29%, respectively. This is the first population-based study that reports the incidence and survival of chronic myelomonocytic leukemia in Spain.

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Abstract

Chronic myelomonocytic leukemia is a very rare blood cancer observed mostly in the elderly. Here we report the incidence trends and survival of patients with chronic myelomonocytic leukemia over a 15-year period (1993-2007). Cases were provided by the population-based Girona Cancer Registry. The crude incidence rate was 0.72/100,000 inhabitants/year. No statistically significant increase in trends was detected over the 15 years. Median overall survival was 28 months although survival markedly decreased with advancing age. The 5-years observed and relative survival were 20% and 29%, respectively. This is the first population-based study that reports the incidence and survival of chronic myelomonocytic leukemia in Spain.

Keywords: Chronic myelomonocytic leukemia, incidence rate, relative and observed survival, population-based cancer registry
Introduction

Chronic myelomonocytic leukemia (CMML) is a very rare haematopoietic disease characterized by myeloproliferative and myelodysplastic features. The classification of CMML within myeloid neoplasms was controversial for many years until its categorization by the World Health Organization (WHO) in 2001 [1]. The new classification considered this disease to fall within an independent group of myeloid neoplasms which share both qualities: proliferation and dysplasia [2-6]. This group of myelodysplastic/myeloproliferative neoplasms comprises, apart from CMML, juvenile myelomonocytic leukemia (JMML), atypical chronic myeloid leukemia (aCML, BCR-ABL1 negative) and myelodysplastic/myeloproliferative diseases, unclassifiable [5-7].

It is known that the median age of CMML diagnosis ranges from 65 to 75 years with a male predominance of 1.5-3.1:1 [2,4,6]. When this disease occurs in children it is called JMML. It usually appears in children under 6 years of age and a similar male predominance is detected, as with CMML [2,4,6].

While information on risk factors is not well defined, it is known that male gender, advanced age, previous exposure to adverse environment substances like carcinogens or ionizing radiation and chemotherapy treatment for a previous cancer may increase the risk of suffering CMML [6,8]. Prognostic factors, on the other hand, have been well described. Some studies have shown that anaemia, presence of circulating immature myeloid cells and percentage of blast in bone marrow can influence the prognosis of CMML, as well as cytogenetic alterations (which occur in 20-40% of cases) and somatic mutations in some genes like TET2, CBL, JAK2, KRAS, RAS, RUNX1 and ASXL1 [2,5,6,9-14].
Although median survival for CMML patients is around 12-24 months, it can vary from 1 to over 100 months due to disease heterogeneity [2,5-7,11].

There are no reliable CMML incidence data because in some epidemiological surveys it is grouped with chronic myeloid leukemia (CML) and in others regarded as myelodysplastic syndrome (MDS). Given that few population based data are reported [15,16], it is important to have more data regarding incidence and survival of this disease to provide clinicians with more useful and reliable information.

The aims of this study were: a) to estimate the CMML incidence trends in the province of Girona during the period 1993-2007, and b) to estimate survival according to sex, age and year of diagnosis.
PATIENTS AND METHODS

Data
Data were extracted from the population-based Girona Cancer Registry (GCR). The GCR is located in the Northeast of Catalonia, Spain, covering a population of 706,185 inhabitants as of the 2007 census [17]. Information sources for the cancer registry are regional and taken from community hospitals, haematology and pathology departments, and death certificates. The completeness of the registry is 96.3%.

Population data used for the statistical analyses were provided by the Institut d’Estadística de Catalunya (Catalonia Statistics Institute or IDESCAT) [17]. We restricted our statistical analysis to the population diagnosed with CMML resident in Girona province from 1993 to 2007. The second edition of Diseases for Oncology (ICD-O-2) [18] was used by the GCR up until 1997 and the third edition of International Classification of Diseases for Oncology (ICD-O-3) [19] has been used since 1998. The ICD-O-2 code for cases diagnosed with CMML before 1998 (code: 9868/3) was converted into ICD-O-3 code (code: 9945/3) after consulting the pathological and haematological results of the initial diagnosis. The GCR used ICD-O-3 classification codes to register haematological malignancies diagnosed between 1998 and 2001 according to proposals included in the WHO classification [20].

Incidence
The mean and the standard deviation (SD) were calculated overall and by sex and compared using a $t$ test. Incidence was calculated as the crude rate (CR), the age-standardized rate for the world standard population (ASRW) and the age-specific rate for 5-years overall and by sex [2,6]. Epidat software was used to compute CR and ASR with a
95% confidence interval (95% CI), using the direct method [21]. The results were expressed in cases per 100,000 inhabitants/year.

In order to compare our results with other international studies related to incidence of CMML, we also calculated the age-standardized rate (ASR) using the European and American populations as standards.

Time trends related to incidence rates by CMML were assessed through the estimated annual percentage change (EAPC) of the incidence standardized rates. The Joinpoint log-linear regression model was used to calculate EAPC with their 95% CI [22]. The standard parametric Fisher test was used to corroborate whether differences in incidence rates between years were statistically significant.

**Survival**

Follow-up time was calculated as the difference between the date of diagnosis and date of death, if the patient was dead, or the end of the follow-up study (December 31st, 2010) if the patient was alive when the period study ended. Vital status of patients was obtained by linking records to the Catalan Registry of Mortality and the National Death Index [23,24].

In order to evaluate and compare survival time, we calculated observed survival (OS) overall, by sex, by age (<75 years and ≥75 years) and by year of diagnosis (1993-1997, 1998-2002 and 2003-2007) [2,4,6]. OS curves were calculated using the nonparametric Fleming-Harrington method because risk was not proportional, and G-rho tests were used to compare the curves between sex and age [25,26]. Analyses were performed using R software. Statistical significance was determined at p=0.05.

Due to the advanced age of patients and competing causes of mortality other than CMML, relative survival (RS) was estimated with 95% CI. It was computed using WAERS [27], a
web-based application developed by the Catalan Institute of Oncology [28] which uses the Hakulinen method to estimate expected survival [29].
RESULTS

During the period 1993-2007, a total of 61 cases of CMML were reported by the GCR. This represented 1.45% (61/4202) of all haematological malignancies diagnosed in Girona province during the same period and 6.53% (61/934) of all myeloid neoplasms.

Incidence

Table 1 shows descriptive results and incidence. Of these patients, 25 were women (40.98%), with a mean age (SD) of 78.64 years (9.13), and 36 were men (59.02%), with a mean age (SD) of 79.03 years (7.31). Differences in age between sex were not statistically significant (p=0.86). A male predominance was found for CMML, with a sex ratio of 1.79, although this was not statistically significant (p=0.88).

CR was higher in men than in women (0.85 and 0.59 respectively). Corresponding overall ASR expressed in 100,000 inhabitants/year was 0.25 for the two sexes (0.34 in men and 0.19 in women). Monitoring incidence time trends by Joinpoint regression there was no evidence of change. EAPC was 3.29% with a 95% CI of -2.09 to 8.96 (data not shown). The standard parametric Fisher test showed a p=0.13, therefore the increase of the rate can be approximated parametrically in a straight line.

As Figure 1 shows, CMML age-specific rate increases with age in both sexes. Under 74 the incidence was similar by sex but for the older age groups the incidence was higher among males than females.
Survival

Five-year OS and RS of patients diagnosed with CMML were 20% and 29%, respectively (Figure 2). In this cohort, the median OS was 28 months (95% CI: 15.90;40.01) (Figure 3A).

No statistically significant difference in survival curves was observed between sexes ($p=0.40$) (Figure 3B). There was a statistically significant difference when comparing OS according to age group ($p<0.001$) (Figure 3C). Better survival was found for patients under 75 (median OS: 64 months) than for patients aged $\geq 75$ (median OS: 19 months). Differences between periods of diagnosis were not statistically significant ($p=0.18$) (Figure 3D). The median OS for patients diagnosed from 1993-1997 was 23 months, compared to 17 months for patients diagnosed from 1998-2002 and 37 months for those diagnosed from 2003-2007.
Discussion

This study describes the incidence and survival rates for patients diagnosed with CMML in the Girona province over the period 1993-2007. This is the first population-based study on CMML in Spain. Although some epidemiological studies reported incidence and survival data of MDS and myeloproliferative neoplasms (MPN), there are very few population-based studies related to CMML. Changes in the classification of CMML resulted in data collection becoming unreliable and data not being properly recorded in population-based cancer registries. Also, the ICD-O-2 did not consider MDS and some MPN malignant, so probability some cancer registries did not record them [18,30,31].

CMML is widely accepted as being a very rare malignancy, with an incidence lower than one case per 100,000 inhabitants/year and an annual average of 4 new cases per year in our region. The incidence of CMML in Girona was very low in the population aged <75 and increased steadily with advancing age. More than 70% of patients were over 75 (Figure 1). This result coincided with the age of patients at time of diagnosis (from 65 to 75 years old) and although there was a male predominance, the difference between sexes was not statistically significant. The observed incidence rate of CMML was similar to rates reported in France and Southeast England. Nevertheless, incidence was higher in Girona than in the US (Table 2) [32-34]. The low incidence in the US is probably a consequence of an underreported registry of CMML cases. Compared to other cancers, CMML is a haematological malignancy diagnosed and managed outside hospitals, and although independent laboratories report cases to local registries, the completeness of case reporting is not well-known.
The median survival of CMML patients is around 12-24 months and even though it can vary from 1 to over 100 months, survival with CMML is extremely poor [2,5-7,11]. In the present study, the median OS was 28 months. There were no differences in survival between men and women or among periods of diagnosis. With regard to the effect of age on survival, we found that survival decreases rapidly with advancing age.

We also reported a 5-year OS of 20% and a RS of 29%. After comparing our results with other international publications we found that there were some variations in RS between different countries. RS observed in Girona was higher than in Southeast England and the US but lower than in France (Table 3) [32-34]. Differences in survival may be due to number of patients, age of population studied, percentage of CMML subtype and consequently percentage of transformations into acute myeloid leukemia (AML) and treatment used in each case. According to the literature, patients with CMML-1 (less than 5% of blasts in PB and less than 10% of blasts in BM) survive between 18 and 20 months, while patients with CMML-2 (peripheral blasts 5-19% and marrow blasts 10-19%) have a slightly lower survival, from 12 to 14 months, as a consequence of the probability of developing AML from 1 to 125 months after diagnosis [2,7,11,35-37]. This transformation occurs in approximately 18% (15-30%) of cases and survival of these patients decreases up to 14 months or less. In this context, AML is called secondary AML (sAML) and has a poorer prognosis than CMML [6,7,36].

Currently, no standardized approach to treatment has been proven to be effective or to modify the pathogenesis of all CMML patients. Allogenic hematopoietic stem cell transplantation remains the only known curative method, but is a possible option in only a minority of patients aged 65-75. Most people who suffer CMML are treated with palliative
drugs and supportive cares such as hydroxyurea, oral etoposide, low-dose citarabine and oral topotecan [2,7,35,37]. Although clinical trials have been carried out, the results are still not as satisfactory as expected for all patients and more research is needed. An example of new treatments recently approved by the Food and Drug Administration (FDA) are hypomethylating agents like azacitidine and decitabine, which have demonstrated anti-MDS activity. These are now being administered for CMML and MDS treatment although results are not well known [38-40].

Some limitations of this study must be considered. Firstly, CMML is a disorder which is difficult to classify and some cases were probably registered as MDS. Secondly, we must take into account that diagnosis methods change and are now more sensitive and precise than some years ago. Thirdly, we must also bear in mind the heterogeneity of the data used, as they are provided by different hospitals and pathology laboratories. Finally, the GCR does not collect clinical data regarding the percentage of blasts to classify CMML into prognostic subtypes (CMML-1 or CMML-2).

**Conclusions**

This is the first population-based study to analyze the incidence and survival rates of CMML in Spain. Taking into account that CMML is a very uncommon blood cancer that affects elderly people, these data are useful in determining the population incidence and especially the associated disease survival rate. Survival is low among people who suffer from CMML and due to the fact that current treatments are not effective, more research is required to improve this situation.
Reference List


Acknowledgements

The authors acknowledge participation of hospitals from the Girona province to provide data to the Girona Cancer Registry. This study was supported with the pre-doctoral grant “Formació Personal Investigador” (FI) from the Autonomous Government of Catalonia.

Funding Source

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Authors’ Contributions

Gemma Osca-Gelis: conception and design of the study, acquisition of data, analysis and interpretation of data. Drafting the article and final approval of the version to be submitted.
Montserrat Puig-Vives: revising the article critically and final approval of the version to be submitted.
Marc Saez: analysis and interpretation of data. Revising the article critically and final approval of the version to be submitted.
David Gallardo: revising the article critically and final approval of the version to be submitted.
Francesc Solé: revising the article critically and final approval of the version to be submitted.
Rafael Marcos-Gragera: conception and design of the study, acquisition of data, analysis and interpretation of data. Drafting the article and final approval of the version to be submitted.

Conflict of interest statement

The authors declare no conflict of interest.
Figure Legend

Figure 1. Age-specific incidence rate of chronic myelomonocytic leukemia by age groups in Girona (Spain), 1993-2007.

Figure 2. Relative and observed cumulative survival of patients with chronic myelomonocytic leukemia in Girona (Spain) 1993-2007, by 5-year time periods.

Figure 3A-D. Cumulative survival curves of patients diagnosed with chronic myelomonocytic leukemia in Girona (Spain) for 1993-2007. A) Global survival curve with 95% confidence interval. B) By sex. C) By age groups (<75 years and ≥75 years). D) By time period (1993-1997, 1998-2002 and 2003-2007)
Figure 1

A graph showing age-specific rates per 100,000 inhabitants-year, with age groups ranging from <55 to >85. The graph compares rates for women, men, and both sexes.
Figure 2

RS (relative survival), OS (observed survival)
Figure 3A-D

A

N at risk

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B

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<tr>
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C

N at risk

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<tr>
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D

N at risk

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<td>10</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>1998-2002</td>
<td>9</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>2003-2007</td>
<td>23</td>
<td>15</td>
<td>2</td>
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Table Legends

Table 1. Descriptive results and incidence rate for cases of chronic myelomonocytic leukemia diagnosed in Girona during the period 1993-2007.

Table 2. Age standardized incidence rate reported in some epidemiological studies of chronic myelomonocytic leukemia: Girona (Spain), South East England, Côte d’Or (France) and the United States. Incidence rates are adjusted by World standard population, European standard population and US standard population.

Table 3. Median observed survival in months and relative survival at 1,3,5 years in percent (95 % confidence interval) of chronic myelomonocytic leukemia in some epidemiological studies: Girona (Spain), South East England, Côte d’Or (France) and United States.
Table 1

<table>
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<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
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<tr>
<td>N</td>
<td>36</td>
<td>25</td>
<td>61</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>79.03 (7.31)</td>
<td>78.64 (9.13)</td>
<td>78.87 (8.03)</td>
</tr>
<tr>
<td>Median age</td>
<td>79</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>&lt;65 years (%)</td>
<td>2.78</td>
<td>4</td>
<td>3.28</td>
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<tr>
<td>65-75 years (%)</td>
<td>19.44</td>
<td>28</td>
<td>22.96</td>
</tr>
<tr>
<td>≥ 75 years (%)</td>
<td>77.78</td>
<td>68</td>
<td>73.77</td>
</tr>
<tr>
<td>CR</td>
<td>0.85</td>
<td>0.59</td>
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N (number of cases), SD (standard deviation), CR (crude rate per 100,000 inhabitants/year).
Table 2

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<tr>
<th>Age standardized incidence rate/100,000 inhabitants/year (95% confidence interval) adjusted by:</th>
<th>Results obtained in this study. Girona 1993-2007 (n=61)</th>
<th>Karen et al. South East England 1999-2001\textsuperscript{33} (n=99)</th>
<th>Maynadiè et al. Côte d'Or (France) 1980-2004\textsuperscript{34} (n=146)</th>
<th>Phekoo et al. United States 2001-2004\textsuperscript{32} (n=2601)</th>
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<td>World standard population</td>
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<tr>
<td>Males</td>
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<tr>
<td>Females</td>
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<tr>
<td>All</td>
<td>0.25 (0.18-0.32)</td>
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<tr>
<td>Sex ratio</td>
<td>1.79</td>
<td>2.16</td>
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<td>European standard population</td>
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<td>Sex ratio</td>
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<td>US standard population</td>
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<td>Sex ratio</td>
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n (number of cases)
Table 3

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<td>78 (67-91)</td>
<td>49 (36-67)</td>
<td>29 (17-49)</td>
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<tr>
<td>Male</td>
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<td>73 (58-91)</td>
<td>45 (27-67)</td>
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<tr>
<td>Female</td>
<td>30</td>
<td>85 (70-100)</td>
<td>58 (39-87)</td>
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n (number of cases), OS (observed survival), RS (relative survival).