The EUTOS population-based registry: Incidence and clinical characteristics of 2904 CML patients in 20 European Countries

The EUTOS population-based registry: Incidence and clinical characteristics of 2 904 CML patients in twenty European Countries.

Short title: Results of a European population-based CML registry

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CONFLICTS OF INTEREST

VSH, MB, JH and DL receive research funding from Novartis. NT and ZS have a consulting or advisory role at Novartis. AC and GG are employed by Novartis. KI has a consulting or advisory role at Amgen and Novartis. BS has a consulting or advisory role at BMS. AB receives funding of travel, accommodations, or expenses from Novartis Oncology, Serbia. RH receives honoraria from BMS and research funding from Novartis and BMS. SB receives honoraria from Novartis, Celgene, and AOP, has a consulting or advisory role at Novartis and Celgene, and receives funding of travel, accommodations, or expenses from Novartis and

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ABSTRACT

This population-based registry was designed to provide robust and updated information on the characteristics and the epidemiology of chronic myeloid leukemia (CML). All cases of newly diagnosed Philadelphia positive, BCR-ABL1+ CML that occurred in a sample of 92.5 million adults living in twenty European countries, were registered over a median period of 39 months. 94.3% of the 2904 CML-patients were diagnosed in chronic phase. Median age was 56 years. 55.5% of patients had comorbidities, mainly cardiovascular (41.9%). High risk patients were 24.7% by Sokal, 10.8% by EURO, and 11.8% by EUTOS risk scores. The raw incidence increased with age from 0.39/100000/year in people 20 to 29 years old to 1.52 in those more than 70 years old, and showed a maximum of 1.39 in Italy and a minimum of 0.69 in Poland (all countries together: 0.99). The proportion of Sokal and Euro score high risk patients seen in many countries indicates that trial patients were not a positive selection. Thus from a clinical point of view the results of most trials can be generalized to most countries. The incidences observed among European countries did not differ substantially. The estimated number of new CML-cases per year in Europe is about 6370.

INTRODUCTION

Chronic myeloid leukemia (CML) is a rare disease which went along with an almost always fatal outcome until a few years ago (1). Though the excellent results of TKI treatment (1-5) are raising the legitimate expectation that a considerable number of patients will achieve a condition of treatment-free remission (TFR), the prevalence of patients with CML, treated with TKIs is expected to increase by about 10% per year so that CML is a challenge for health care systems worldwide (4-7). With average TKI treatment costs of between forty and seventy thousand Euros per patient per year in Europe the challenge is how to optimize treatment for patients' maximum benefit with an affordable allocation of the resources (4-8).

The information on the course of CML is based on studies reporting the results of treatment, being company-sponsored approval studies (9-13), investigator-sponsored therapy studies (14-17), and single reference centre database reports (18,19). All current policies of treatment, and the debates about different policies, are based on these studies, which have been performed according to Good Clinical Practice, or in well-reputed reference centres. Moreover, all treatment studies, particularly the company-sponsored studies, declared several limitations of patient eligibility, with many exclusion criteria. Thus patients admitted to these trials cannot be considered to represent the typical CML patients. Little information is available on the incidence and prevalence of the disease and on patients' baseline characteristics outside treatment studies. Therefore it is even more important to know the incidence of the disease and the baseline characteristics of all CML patients regardless of the patient's involvement in any clinical trial. For these purposes, the European LeukemiaNet (ELN) designed and conducted a project of a population-based European Registry of CML.

MATERIAL AND METHODS

This work was set up inside the framework of the European LeukemiaNet which is a network of excellence that was initially funded by the European Union in 2004. The ELN started a registry of CML patients who were newly diagnosed between 2002 and 2006 and were treated frontline with imatinib (21,22). In 2007, Novartis Oncology Europe joined ELN and supported a prospective study called EUTOS (European Treatment and Outcome Study of CML), with specified goals, including the establishment of a comprehensive prospective, population-based, European registry of newly diagnosed CML patients.

Study protocol

A study protocol for this strictly observational study was written and approved in agreement with the national laws and regulations by Ethic Committees and other competent authorities in all participating countries. The study was non-interventional and there were no exclusion criteria, apart from age (< 18 years old). Informed consent was provided according to the laws and regulations in the participating countries.

As logistic and financial limitations did not allow to register all incident CML-patients in all European countries, the protocol asked the "smaller" countries (with less than 10 million inhabitants) to survey their whole territory whenever possible, while the "bigger" countries (with more than 10 million inhabitants) were requested to limit the registration to one or more well defined regions, up to a maximum total of altogether 10 million inhabitants. Sweden, Slovakia, Latvia, Lithuania, Estonia, Slovenia, Croatia and Cyprus were able to cover all their respective territories. Spain, France, Italy, UK, Germany, the Netherlands, Austria, Poland, Serbia, Russia, Czech Republic and Finland limited the registration to one or more regions

(Table 1). In the other European countries it was not possible to set up a registry fulfilling the population-based requirements.

In Sweden, the Czech Republic and Germany the registration was based on already existing registries. In Sweden, the registration of all newly diagnosed cases of CML was already required by law since 2002 (20). In all the other countries, the registration was based on the active participation of hematologic and oncologic centres and physicians. Pathologic and laboratory databases were used throughout, but all newly diagnosed patients were registered by clinical institutions, so as to provide not only the baseline characteristics but also to collect follow up information.

Pseudonymised baseline and follow-up data were recorded, including demographic, clinical, hematologic, cytogenetic, and molecular variables using a web-based eCRF-System at ELN's Data Centre in Munich. The clinical and hematologic data used for the calculation of the prognostic scores had to be measured at diagnosis, prior to any treatment (21, 23, 24). To achieve completeness of incident CML cases, it was emphasised that every newly diagnosed case had to be registered, even if some baseline data were missing.

The phases of the disease, chronic, accelerated, and blastic (CP, AP, BP) were defined according to ELN (4).

Statistics

To summarize patients' characteristics, medians and percentages were calculated. Raw and standardized incidences were computed and adjusted to the registration period so the incidences are given per 100 000 inhabitants per year per region or country. For standardization the European standard population was used (25). The registry and the standard population were truncated so only patients from 20 years on were included for the calculation of incidences. Population data from the United Nations database was used for calculations in

countries that were covered nationwide, while the study groups provided the population numbers of the specified regions for countries that were observed partially.

All calculations were performed using SAS Version 9.2 software (Cary, NC, USA) and R version 3.0.1. Data collection, processing and all statistical analyses were exclusively carried out in the data center at the Department for Medical Information Sciences, Biometry, and Epidemiology of the Ludwig- Maximilians-Universitaet in Munich, Germany. Data from 2008 to 2011 from the US *Surveillance, Epidemiology, and End Results Program* (SEER) were processed using the National Cancer Institute SEER*Stat software version 8.1.5.

RESULTS

Countries, regions, registration time, number of inhabitants, and number of newly diagnosed CML patients ≥ 20 years old are shown in Table 1. There were altogether 92 526 127 people ≥ 20 years old living in the observed areas and the total number of newly diagnosed CML-patients with information on age and sex was 2 904, of those 2 887 were ≥ 20 years old. Registration time ranged from 12 to 60 months (median 39 months) in the period between January 2008 and December 2012.

Baseline characteristics

Age and sex distribution in all countries pooled together are shown in Table 2. Males accounted for 53.7% of all patients, with a male to female ratio of 1.16. Median age was 55 years, 55 in males, and 57 in females. Median age and sex distribution are shown country-wise in Table 1. There was considerable variation seen in the proportion of males, from a minimum of 38.8% of males in France to a maximum of 74.2% in Estonia, two countries where the number of registered cases was small. Considering only the countries with more than 100 registered patients, the proportion of males ranged from 48.8% in Russia to 58.8% in Sweden. The median age of newly diagnosed patients ranged from 44 to 64 years in males, from 52 to 65 years in females, and from 50 to 64 years overall. Median age was particularly low in Russia (50 years) and particularly high in Estonia, Germany and Sweden (61-64 years).

At diagnosis, 94.3% of patients were in CP, 3.5% in AP, and 2.2% in BP. Eighteen percent of all patients were current smokers, and 16% were former smokers. There were 28.7% of patients with one comorbidity recorded, 15.3% with two, and 11.5% with more than two comorbidities (Table 3). Hypertension (25.7%), other cardiovascular disorders (17.2%), and

diabetes mellitus (9.5%) were the most frequent comorbidities. Laboratory data, spleen size and prognostic score distribution of CP patients are shown in Table 3. Spleen was not palpable in 53.5% of the patients, and a big spleen (≥ 10 cm below costal margin) was reported for 15.2% of patients only. Variant translocations and additional chromosomal abnormalities in Ph+ cells were reported for 3.7% and 9.4% of patients, respectively. The transcript type was b3a2, or mixed (b3a2/b2a2) in 56.6%, and b2a2 in 38.9% of patients. Not otherwise specified transcripts were reported in 4.5% of the patients.

By Sokal risk score, 34.5% of all patients were low risk and 24.7% were high risk. By EURO score, 37.4% of all patients were low risk and 10.8% were high risk. By EUTOS score, 11.8% of all patients were high risk.

Incidence

The raw incidences of CML in all countries, stratified by sex and age, are shown in Table 4 and Figure 1. For both sexes, the yearly incidence rose from a minimum of 0.39 new cases per 100,000 inhabitants (0.47 in males, 0. 29 in females) in very young adults (20-29 years old) to a maximum of 1.52 (2.08 in males, and 1.18 in females) in senior adults of 70 years and more. The incidence was always higher in males than in females in any age group.

The standardized incidence in all countries was 1.10 for males, and 0.82 for females.

The raw and the standardized incidences are reported country-wise in Table 1. The raw incidences ranged from 0.69 in Poland to 1.39 in Italy. The standardized incidences ranged from 0.70 in Poland, the UK and Austria to 1.28 in Italy. Standardized and raw incidences were always higher in males than in females, with the exception of France regarding standardized incidence and France and Finland for the raw incidences. In both countries,

however, data were collected in small regions. A particular regional clustering of high or low incidences could not be seen.

DISCUSSION

To our knowledge our study is the first one which covered many European countries and searched for incident adult cases of CML using a uniform approach and highly standardized definitions. The raw incidence in the 20 participating countries varied between 0.69 to 1.39/100 000/year, the male to female ratio was 1.16:1, and the median age was 55 years. About 95% of the patients were diagnosed in chronic phase CML. There was no hint for a particular regional pattern of the CML-incidences.

Limitations

This study has got two characteristics that may have led to underreporting, namely the registration through clinical institutions and the short registration period. Registering through clinical institutions, was intended as clinical and outcome data were collected additionally. But clinical institutions are not always trained in epidemiological surveys and at least some patients may have escaped their attention for various reasons. Luckily, in Sweden, the registration of all new cases of CML was already statutory (20), so that Swedish data provided a sort of completeness control for the data of all the other countries. Comparing the Swedish incidences to the incidences of the EUTOS registry distinct differences are only notable in the very senior male population, where the sample size was rather small (Figure 1). Different health care and reimbursement systems which may result in different health care seeking behaviours and diagnostic ambition were beyond of the scope and the control of our study. Taken together, due to these biases, some cases of CML may have been missed in particular in the higher age groups. Thus all the reported figures must be considered an approximate, and a minimum, estimate of the true CML incidence. Moreover, caution in the evaluation of the differences between countries is advised, in particular when countries with

different socio-economic profiles are compared. With these limitations, the EUTOS study is unique as it provides the current baseline characteristics of a large number of newly diagnosed, Ph+, BCR-ABL1+, patients, for many countries.

Strengths

The size of the sample, accounting for about 1/5 of European inhabitants in that age group, should provide sufficiently representative and reliable estimates. The identification of the disease by molecular or cytogenetic methods was planned to avoid confusion with Ph- chronic myeloproliferative neoplasms (Ph- CMPN), with chronic myelomonocytic leukemia (CMML), and with some cases of myelodysplastic syndrome (MDS). Thus this requirement is a strong point of our study as it guarantees for valid diagnoses. The importance of cytogenetic and molecular definition of diagnosis is underscored by US SEER data, reporting a very high incidence, particularly in the elderly, of newly diagnosed cases without cytogenetic or molecular confirmation, versus a surprisingly low incidence of cases with confirmed BCR-ABL1+ leukemia (Figure 1).

Baseline characteristics

The first interesting finding is the proportion of patients with a diagnosis in AP and in BC. They are a minority, but they account for more than 5% of all cases. Moreover, in patients presenting in CP, the frequency of other chromosome abnormalities, either variant translocations or clonal chromosome abnormalities in Ph+ cells (CCA/Ph+), was slightly higher than 10% overall, and some CCA/Ph+ have been shown to be prognostically relevant (26, 27). Another interesting finding was the frequency of splenomegaly. In textbooks, CML is described as a disease characterized by splenomegaly, with some emphasis on the big

volume of the spleen. Nowadays, in about 50% of newly diagnosed patients, the spleen is not even palpable, and only in about 15% the spleen is large.

A comparison of EUTOS baseline characteristics with the data of pivotal treatment studies confirms that the patients who are enrolled in prospective treatment studies are somehow different from, and not fully representative of, patients in routine care, and that some of them are systematically underrepresented. The difference is particularly relevant for the main company-sponsored phase III-trials that evaluated the therapeutic effects of TKIs to obtain the marketing authorisation from major drug authorities like the FDA and EMA. (9-13) (Table 5). The main difference concerned age, with a median of 55 years in the EUTOS population and of 46 to 51 years for company-sponsored trials.

The number of missing data in Table 4 underscores that many baseline characteristics important for prognostic calculation, including spleen size and differential (particularly blast cells, basophils and eosinophils) were not reported in some company-sponsored trials. The WBC count as reported in company-sponsored trials was so low that it may be explained only assuming that in those studies the WBC count was not recorded baseline, prior to any treatment, as in EUTOS, but only after some antileukemic treatment, most likely hydroxyurea. Since the calculation of all prognostic scores requires that all hematologic values are recorded prior to any treatment it is not clear how the prognostic scores could be calculated in those company-sponsored trials.

However, it is a clinically important finding of our study that considering the prognostic profiles the results indicate that the patients recruited for the randomized trials were not a particularly positive selection of the population despite the difference in age: Sokal high risk patients account for 24.7% of patients in the registry and for 17.9% - 27.7% in the randomized trials. Thus one may safely assume that the results of the randomized trials are generalizable to many countries. Unfortunately, the Euro score is only reported in the IRIS and the

DASISION reports (10.1% and 19.1% Euro high risk patients), but those also support the finding of generalizability with 10.8% of Euro high risk patients in the EUTOS registry. This assessment is supported by the findings of Gambacorti-Passerini et al. (36) who reported highly similar effectiveness data for CML-patients in routine health care compared to randomized trials. Höglund et al. (20) also reported that the relative survival of 779 CML-patients of the Swedish CML-registry was close to 1.0 at 5 years for patients younger than 60 years and 0.9 for those aged 60 to 80 years.

A small sample size can impair the valid detection of small differences between the incidences for rare diseases, and could result in an artificial magnification of differences. For these reasons, we limited the comparison of the prognostic profiles to the countries with more than 100 registered new cases. In these countries, Sokal and EURO low risk patients roughly ranged between 30 and 40%, with the notable exceptions of Spain, where they were 47.3% Sokal and 48.7% (EURO) and of Sweden with 23.0% (Sokal). In the same countries, the proportion of high risk patients ranged roughly from 20 to 30% for Sokal, from 9 to 16% for EURO, and from 10 to 20% for EUTOS.

The exception was Spain with just 12.6% high Sokal, 1.8% high EURO, and 3.2% high EUTOS. In contrast, the UK had the highest proportion of high risk patients, 34.2% by Sokal, 17.5% by EURO, and 23.2% by EUTOS.

All together these data suggest that in some countries, like Spain and UK, CML present with different prognostic characteristics, or is diagnosed at different times of the course of CML.

Incidences

A comparison of the raw and of the age standardized incidences in EUTOS and earlier studies is shown in Table 6 (20, 28-35). For males and females all together, two European studies

(31,32) reported a raw incidence of 1.10 and 1.20. The Swedish registry (20) reported a raw incidence of 0.97 (1.07 in males, and 0.88 in females), very close to EUTOS. Studies performed in selected regions of Spain, France, England and Germany (28-30, 33, 34), reported a raw incidence ranging from 0.79 in Germany to 1.15 in Spain. Few data were available for the standardized incidence adjusted for age, either European or World, with values less than 1.00 in females, and ranging from 0.72 to 1.40 in males (Table 5). A more detailed analysis of the incidence by age is available only from the United States (SEER) (35) and the Swedish registries (20). In all age groups, the incidence was lower in the United States than in Sweden and in EUTOS, when using only cases with ICD-O-3 code 9875 which is in use since 2001 and requires the patient to be BCR-ABL1+ (Figure 1). Incidences including also patients with ICD-O-3 code 9863 - who are not confirmed to be Ph+ and /or BCR-ABL1+ - are much higher. It is difficult to conclude that the reported differences between Europe and US reflect a truly different incidence. Underreporting of cytogenetic or molecularly defined cases is more likely.

This sample of 92.5 million people was taken from 20 countries with about 447.6 million people ≥ 20 years old. In the other 19 European countries that were not sampled, the number of inhabitants ≥ 20 years old is about 130 millions. Therefore, in Europe, including Russia but not Turkey, the total number of people ≥ 20 years old is about 575.5 millions. Extrapolating the raw incidence that was calculated in 20 countries from 92.5 million people, the number of newly diagnosed cases of Ph+, BCR-ABL1+, CML should approximate 6370 per year. With an expected yearly death rate of about 2% per year (1-5), the prevalence of CML will grow considerably in the future (6,7).

This trend underscores the importance of setting and maintaining this kind of registries, in order to plan the management of the disease. The establishment of dedicated referral centres could help to limit the costs of therapy and therapy monitoring. Epidemiologic studies are

essential for setting strategies for long/term treatment, including drug choice and drug dose, and particularly the strategies for the achievement of a condition of treatment-free remission and they are the basis of evidence-based health care. Finally, registries like this allow to assess the generalizability of the results of clinical trials which is an important feature in these times of strict adherence to evidence-based medicine and budget restrictions.

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FIGURE LEGENDS

Figure 1: Age- and sex-stratified estimations of incidence of Ph+ and /or BCR-ABL1+ CML from the EUTOS and the Swedish CML Registry (20), and of BCR-ABL1+ CML from SEER (35).

TABLE LEGENDS

Table 1: Countries and country regions of registration, number of inhabitants (≥ 20 years old), registration time (months), and number of newly diagnosed Ph+ and/or BCR-ABL1+ cases, all phases (chronic, accelerated, and blastic). Distribution by sex and age. Raw incidence and standardized (Old European Standard Population) incidence of newly diagnosed CML patients (≥20years), per 100,000/year.

Table 2: All countries, all phases (chronic, accelerated, blastic). Distribution of newly diagnosed patients by age and sex.

Table 3: All countries, chronic phase, baseline characteristics, recorded prior to any therapy (n=2 388).

Table 4: Raw incidences for all countries together per 100,000 inhabitants stratified by age and sex.

Table 5: Baseline characteristics of company-sponsored, registration studies (IRIS, TOPS, ENESTnd, DASISION, BELA). Comparison with EUTOS data. Notice that in all company-sponsored studies the reported white blood cell count was very low, suggesting that it was not recorded baseline, prior to any therapy. NR = Not Reported

Table 6: Raw and standardized incidence of CML, as reported in US (SEER data from 2008-2011), in Europe, and in this EUTOS study.

Country	Regions	No. inhabitants ≥20 years old	Registration time (months)	No of cases	Male %	Male, median age (years)	Female, median age (years)	Total, median age (years)	Males, raw incidence	Males, standardised incidence	Females, raw incidence	Females, standardised incidence	Males and females, raw incidence	Males and females, standardised incidence
Austria	Upper Austria, Salzburg, Tirol, Voralberg, Styria	3 350 069	13-36 (median 25)	55	61.8	57	59	57	0.91	0.91	0.53	0.50	0.71	0.70
Croatia	Whole country	3 493 000	38	126	55.6	54.5	57	57	1.34	1.30	0.96	0.89	1.14	1.10
Cyprus	Whole country	660 000	18	9	66.7	52	55	53	1.27	1.33	0.58	0.63	0.91	0.98
Czech Republic	Olomouc, Prague region, Brno region, Moravian-Silesian, Hradec Kralove, Pardubice, Plzen, Karlovy Vary, Usti nad Labem, South Boemia	7 563 278	24-42 (median 41)	308	55.2	55	58	56	1.38	1.36	1.06	1.01	1.22	1.19
Estonia	Whole country	1 055 000	35	31	74.2	59	65.5	64	1.67	1.74	0.47	0.45	1.01	1.10
Finland	Helsinki region	1 225 661	39	38	47.4	54	56	55.5	0.95	0.94	0.96	0.88	0.95	0.91
France	Poitou-Charentes	1 356 836	43	49	38.8	59	58.5	59	0.82	0.76	1.18	1.11	1.01	0.93
Germany	Oberbayern	3 710 064	36	139	49.6	63	60	61	1.28	1.12	1.22	1.09	1.25	1.11
Italy	Emilia-Romagna, Sicily	7 294 154	17-60 (median 46)	356	52.5	56	60	57	1.53	1.40	1.27	1.16	1.39	1.28
Latvia	Whole country	1 797 000	36	42	52.4	50	62.5	52.5	0.91	0.93	0.67	0.61	0.78	0.77
Lithuania	Whole country	2 550 000	36	81	48.2	56	52	54	1.12	1.15	1.01	1.04	1.06	1.10
Netherlands	Amsterdam region, Rotterdam region. South region	4 819 282	45	179	57.0	50	56	54	1.14	1.10	0.82	0.79	0.98	0.94
Poland	Kujawsko-Pomorskie, Pomorskie, Warmińskie, Małopolskie, Podkarpackie, Świętokrzyskie	9 494 215	41	225	49.3	56	54.5	55	0.71	0.74	0.67	0.66	0.69	0.70
Russia	St. Petersburg, Leningrad region, Mordovia, Kirow, Perm, Bryansk, Irkutsk, Chita	13 097 675	28-39 (median 38)	337	48.4	44	54	50	0.89	0.90	0.75	0.73	0.81	0.82

Serbia	Belgrade city and district, East Serbia, West Serbia, South Banat	3 059 053	41	96	56.3	58	52.5	57	1.06	1.01	0.78	0.76	0.92	0.89
Slovakia	Whole country	4 263 268	39	147	53.6	57	56.5	57	1.18	1.22	0.94	0.94	1.06	1.08
Slovenia	Whole country	1 639 000	35	44	52.3	64	59	59.5	1.00	0.94	0.85	0.81	0.92	0.87
Spain	Comunidad de Madrid, Castilla-La Mancha, Aragon	7 942 014	32-36 (median 35)	249	58.2	51	56.5	54	1.30	1.31	0.88	0.81	1.08	1.06
Sweden	Whole country	7 136 000	41	264	58.7	62	62	62	1.29	1.17	0.88	0.75	1.08	0.96
United Kingdom	North Wales, Lancashire and South Cumbria, Merseyside and Cheshire, Yorkshire	5 592 562	31-40 (median 35)	112	49.1	58	58	58	0.76	0.71	0.73	0.69	0.75	0.70
Total	20 countries 49 regions	92 526 127	39	2887	53.7	55	57	56	1.12	1.10	0.88	0.82	0.99	0.96

Table 1: Countries and country regions of registration, number of inhabitants (≥ 20 years old), registration time (months), and number of newly diagnosed Ph+ and/or BCR-ABL1+ cases, all phases (chronic, accelerated, and blastic). Distribution by sex and age. Raw incidence and standardized (Old European Standard Population) incidence of newly diagnosed CML patients (≥20years), per 100,000/year.

Age, years	Male N°	Male %	Female N°	Female %	Total N°	Total %
18-29	139	8.9	78	5.8	217	7.5
30-39	199	12.8	141	10.5	340	11.7
40-49	262	16.8	229	17.0	491	16.9
50-59	347	22.3	304	22.6	651	22.5
60-69	274	17.6	283	21.0	557	19.2
70-79	246	15.8	215	16.0	461	15.9
80-89	85	5.5	90	6.7	175	6.0
90-99	6	0.4	6	0.5	12	0.4
Total	1 558	100 %	1 346	100 %	2 904	100 %

Table 2: All countries, all phases (chronic, accelerated, blastic). Distribution of newly diagnosed patients by age and sex.

Hematologic values		**Spleen**		**Comorbidities (n=2360)**	
Hb (g/dl), males , median (n=1 286)	12.5	**Spleen, cm[@]**, median (n=2 331)	0	Hypertension	25.7%
Hb, males, < 8.0	3.0 %	Spleen, cm[@], 0 (non palpable)	53.5 %	Cardiovascular disorders	17.2%
Hb, males, 8.0 - 12.0	39.7 %	Spleen, cm[@], > 0 – 4	19.6 %	Diabetes mellitus, all types	9.5%
Hb, males, > 12.0	57.3 %	Spleen, cm[@], > 4 - < 10	11.8 %	Neurologic disorders	6.9%
Hb (g/dl), females, median (n=1 095)	11.7	Spleen, cm[@], ≥ 10	15.2 %	Behaviour disorders	2.3%
Hb, females, < 8.0	5.1 %	**Cytogenetic data**		Chronic renal disease	2.6%
Hb, females, 8.0 - 11.0	32.9 %	CCA/Ph+ (n=2 018)	9.4 %	Chronic liver disease	2.2%
Hb, females, > 11.0	62.0 %	Variant translocations (n=2 057)	3.7 %	Others, or unspecified	31.7%
Platelet count, x 10^9/L, median (n=2 381)	395.0	**Molecular data - Type of transcript (n=1 533)**			
Platelet count, x 10^9/L, < 150	5.9 %	b2a2	38.9 %	Patients without comorbidities	44.5%
Platelet count, x 10^9/L, 150 - < 450	52.0 %	b3a2 + b2a2/b3a2	56.6 %	Patients with one comorbidity	28.7%
Platelet count, x 10^9/L, 450 - < 1000	34.7 %	Other	4.5 %	Patients with two comorbidities	15.3%
Platelet count, x 10^9/L, ≥ 1000	7.4 %			Patients with > 2 comorbidities	11.5%
WBC count x 10^9/L, median (n=2 388)	84.6				
WBC count x 10^9/L, < 50	32.7 %	***Sokal Score (n=2 300)***		**ECOG/WHO Score (n=2 280)**	
WBC count x 10^9/L, 50 - < 100	23.0 %	Sokal Low	34.5 %	0 – Asymptomatic	57.1 %
WBC count x 10^9/L, 100 - < 200	24.1 %	Sokal Intermediate	40.8 %	1 – Symptomatic, compl. ambulatory	37.0 %
WBC count x 10^9/L, ≥ 200	20.3 %	Sokal High	24.7 %	2 – Symptomatic, < 50 % in bed/day	4.2 %
Blast cells, %, median (n=2 356)	1.0	***EURO Score (n=2 292)***		3 – Symptomatic, > 50 % in bed/day	1.2 %
Basophils, %, median (n=2 359)	3.0	EURO Low	37.4 %	4 - bedbound	0.5 %
Eosinophils, %, median (n=2 353)	2.0	EURO Intermediate	51.8 %		
		EURO High	10.8 %		
		EUTOS Score (n=2 307)			
		EUTOS Low	88.2 %		
		EUTOS High	11.8 %		

@ cm below costal margin

Table 3: All countries, chronic phase, baseline characteristics, recorded prior to any therapy (n=2 388).

Age group	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Male	0.31	0.63	0.77	0.69	0.97	0.99	1.30	1.60	1.56	1.49	2.28	2.09	2.01	1.52
Female	0.29	0.30	0.46	0.59	0.81	0.88	1.07	1.29	1.36	1.35	1.52	1.11	1.19	0.62

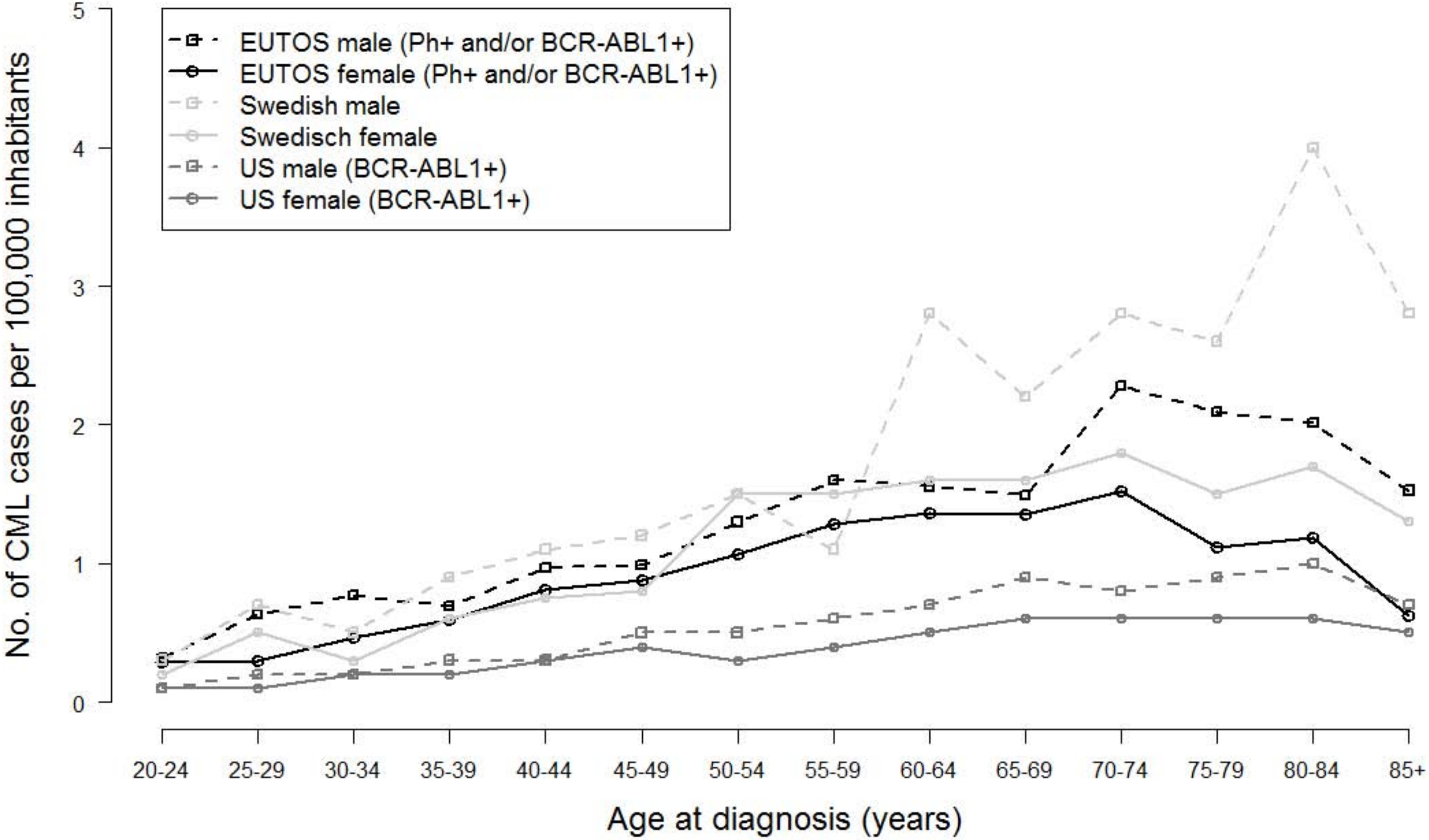
Table 4: Raw incidences for all countries together per 100,000 inhabitants stratified by age and sex.

	IRIS (9)	**TOPS (10)**	**ENESTnd (11)**	**DASISION (12)**	**BELA (13)**	**EUTOS Pop.-based**
No. pts	1106	476	846	519	502	2904
Males	58.9%	56.1%	58.0%	59.2%	56.6%	54.0 %
Age, years, median	51	47	47	46-49	47-48	55.8
Age ≥ 60 years	21.9%	NR	NR	NR	NR	40.1 %
Age ≥ 65 years	NR	NR	NR	8.5%	NR	29.2 %
Spleen palpable	25.0%	NR	NR	NR	NR	46.5 %
Spleen, median, cm	NR	NR	NR	NR	NR	0
Spleen ≥10 cm	6.0%	NR	12.4%	NR	NR	15.2 %
Plt, $x10^9$/L, median	336-340	NR	374-424	390-448	386-451	395.0
Hb, g/dl, median	12.8-13.0	NR	12.0	NR	NR	12.1
WBC, $x10^9$/L, median	17.9-20.2	NR	23-26	23.5-25.1	21.7-23.5	84.6
Blast cells, %, median	0	NR	NR	1.0	NR	1.0
Basophils, %, median	3.0	NR	NR	4.0	NR	3.0
Eosinophils, %, median	NR	NR	NR	NR	NR	2.0
Sokal, low	50.3%	41.4%	36.6%	NR	35.3%	34.5%
Sokal, high	20.3%	24.2%	27.7%	NR	17.9%	24.7%
EURO, low	45.1%	NR	NR	33.3%	NR	37.4%
EURO, high	10.1%	NR	NR	19.1%	NR	10.8%
CCA/Ph+	10.3%	NR	12.9%	NR	NR	9.4 %

Table 5: Baseline characteristics of company-sponsored, registration studies (IRIS, TOPS, ENESTnd, DASISION, BELA). Comparison with EUTOS data. Notice that in all company-sponsored studies the reported white blood cell count was very low, suggesting that it was not recorded baseline, prior to any therapy. NR = Not Reported

Country	No people	No cases	Observation time (years)	Raw Incidence per 100,000 / year			Standardized Incidences European Standard Pop.			Standardized World Standard Population		
				Males	Females	All	Males	Females	All	Males	Females	All
USA (SEER) (35)	62 m	1 352	4	0.63	0.46	0.55	0.64	0.44	0.53	0.58	0.40	0.49
EUROPE (31)	~30% EU	2 468	3	1.23	0.98	1.10						
EUROPE (32)	NR	10 047	25	1.40	1.10	1.20						
SWEDEN (20)												
FRANCE (33)	0.51 m	141	25	1.11	0.70	0.90						
SPAIN (34)	0.73 m	102	15			1.15	1.13	0.82	0.96			
UK (28)	11-16 m	NR	10				1.20	0.76		0.72	0.47	
England (29)	5.5 m	180	2	2.06	1.39		1.34	0.87		1.02	0.67	
GERMANY (30)	9.2 m	218	3	1.01	0.58	0.79						
EUTOS	92.5 m	2 957	1-5 (median 3.2)	1.12	0.88	0.99	1.10	0.82	0.96	0.99	0.75	0.87

Table 6: Raw and standardized incidence of CML, as reported in US (SEER data from 2008-2011), in Europe, and in this EUTOS study.


EUTOS male (Ph+ and/or BCR-ABL1+)
EUTOS female (Ph+ and/or BCR-ABL1+)
Swedish male
Swedisch female
US male (BCR-ABL1+)
US female (BCR-ABL1+)
No. of CML cases per 100,000 inhabitants
0
1
2
3
4
5
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85+
Age at diagnosis (years)