Article

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Abstract

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Reference

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Survival of European patients diagnosed with myeloid malignancies: a HAEMACARE study

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ABSTRACT

Population-based information on the survival of patients with myeloid malignancies is rare mainly because some entities were not recognized as malignant until the publication of the third revision of the International Classification of Diseases for Oncology and World Health Organization classification in 2000. In this study we report the survival of patients with myeloid malignancies, classified by updated criteria, in Europe. We analyzed 58,800 cases incident between 1995 to 2002 in 48 population-based cancer registries from 20 European countries, classified into HAEMACARE myeloid malignancy groupings. The period approach was used to estimate 5-year relative survival in 2000-2002. The relative overall survival rate was 37%, but varied significantly between the major groups: being 17% for acute myeloid leukemia, 20% for myelodysplastic/myeloproliferative neoplasms, 31% for myelodysplastic syndromes and 63% for myeloproliferative neoplasms. Survival of patients with individual disease entities ranged from 90% for those with essential thrombocythemia to 4% for those with acute myeloid leukemia with multilineage dysplasia. Regional European variations in survival were conspicuous for myeloproliferative neoplasms, with survival rates being lowest in Eastern Europe. This is the first paper to present large-scale, European survival data for patients with myeloid malignancies using prognosis-based groupings of entities defined by the third revision of the International Classification of Diseases for Oncology/World Health Organization classifications. Poor survival in some parts of Europe, particularly for treatable diseases such as chronic myeloid leukemia, is of concern for hematologists and public health authorities.

Introduction

Large-scale, population-based information on the survival of patients with myeloid malignancies is scarce. This is mainly due to under-recognition of these diseases in past classifications. The second revision of the International Classification of Diseases for Oncology (ICD-O-2), published in 1990, still considered that myelodysplastic syndromes (MDS) and myeloproliferative disorders were benign and they were only recognized as malignant in the third revision (ICD-O-3).[1] There were also coding difficulties associated with many of these conditions, which further discouraged their registration by cancer registries. For many years, in fact, acute (AML) and chronic myeloid leukemia (CML) were the only myeloid conditions considered malignant; the latter is caused by the t(9;22)(q34;q11) translocation resulting in the easily recognizable Philadelphia chromosome.

This situation was eased after correspondences were established between the ICD-O-3 codes and the World Health Organization (WHO) classifications of hematologic malignancies of 2001[2] and 2008.[3]

The WHO classifications[2,3] exploit many different tumor characteristics but are based fundamentally on cell lineage, reinforcing the distinction between lymphoid and myeloid neoplasms. This distinction was often ignored in past epidemiological studies, which lumped several entities together as 'leukemias'.[4,5] It is also important to distinguish chronic from acute forms of these diseases, as their clinical features, treatments and public health implications differ considerably.

The restricted population-based information that is available on morphological subgroups of myeloid malignancies mainly comes from a few specialized registries of hematologic malignancies.[6,7-9] The fact that these registries are few

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and far between makes comparisons of survival of patients with these diseases across regions and over time problematic. These problems are compounded by the classification difficulties mentioned above, and consequent heterogeneity of disease definitions between countries, treatment centers and cancer registries.

HAEMACARE is a European project that was set up to improve the standardization and availability of population-based data on hematologic malignancies.[10] Under the aegis of this project, hematologists, pathologists and epidemiologists from several European countries reached a consensus on the grouping of myeloid malignancies (as defined by ICD-O-3 morphology codes and WHO nomenclature[1-3]) into larger categories based on similarity of prognosis and, therefore, useful for epidemiological, clinical and public health purposes. The resulting HAEMACARE myeloid malignancy grouping system is analogous to that proposed by the Pathology Working Group of the International Lymphoma Epidemiology Consortium for lymphoid neoplasms.[11,12]

The aim of the present study was to estimate survival of patients with myeloid malignancies alive at some point in 2000-2002, using data from European population-based cancer registries, with malignancies grouped according to the HAEMACARE system. We produced estimates of 5-year relative survival for these disease groupings, by age at diagnosis, and European region.

Design and Methods

Cases and HAEMACARE groupings

We initially considered the 58,800 cases of myeloid malignancy diagnosed between 1995 and 2002, archived in the EUROCARE-4 database,[13] and contributed by 48 cancer registries in 20 European countries.

We grouped these countries into five European regions: Northern Europe (Iceland, Norway, Sweden), UK and Ireland (England, Northern Ireland, Scotland, Wales, Ireland), Central Europe (Austria, France, Germany, Switzerland, the Netherlands), Southern Europe (Italy, Malta, Slovenia, Spain), and Eastern Europe (Czech Republic, Poland, Slovakia). The distribution of these cases by country and cancer registry, with selected data quality indicators, is shown in Table 1.

We next selected the cases to be analyzed based on cancer registry data quality.[14] We included in the analyses only cancer registries with: (i) over 70% of cases microscopically verified; (ii) less than 15% of cases discovered only at autopsy or on the death certificate; and (iii) less than 30% of cases with unspecified morphology (ICD-O-3 morphology codes 9800, 9801, 9805 and 9860). This resulted in 50,328 cases from 42 cancer registries in 17 European countries. These cases are listed in Table 2 by ICD-O-3 code and WHO description, grouped into five major HAEMACARE categories: acute myeloid leukemia (AML), myeloproliferative neoplasm (MPN), myelodysplastic syndrome (MDS), myelodysplastic/myeloproliferative neoplasm (MDS/MPN), and myeloid malignancy of unknown type (leukemia NOS and myeloid leukemia NOS).

AML was divided into four HAEMACARE subgroups: AML with recurrent cytogenetic abnormalities, AML with multilineage dysplasia, AML therapy-related and AML other. The 'AML other' group was subdivided according to lineage, proportion of blast cells and presence of myelofibrosis (9931/3). MPN were divided into CML and three morphological subgroups.

The study protocol required that morphology be coded according to ICD-O-3; however, cases diagnosed before the adoption of the ICD-O-3 (about year 2000 by most registries) were originally coded according to ICD-O-1 or ICD-O-2. These codes were converted into ICD-O-3 using IARC and EUROCARE rules. However conversion was not always exact, because new AML entities were introduced into the ICD-O-3 based on cytogenetic and immunochemical characteristics not available in the past. Cases not classifiable into ICD-O-3 entities were converted to AML NOS, which formed a high proportion of AML in the present study.

The ICD-O-3 classification does not differ from ICD-O-2 for AML and myeloproliferative disorders and, therefore, the annual number of patients diagnosed with these conditions before or after the introduction of the ICD-O3/WHO in 2000 is fairly constant. However changes introduced by ICD-O-3 for MDS and MDS/MPN are reflected in an increase in the annual number of cases since 2000. For MDS 50% and for MDS/MPN 43% of the total cases included in the study (1995-2002) were diagnosed in 2000-2002.

Before 2001, refractory anemia with excess blasts in transformation (9984/3) was considered an MDS. In the WHO classification[3] the number of blast cells to define AML decreased from 30% to 20% so that some conditions previously considered MDS were included with the AMLs. In the present study we grouped these cases as AML with multilineage dysplasia (9895/3) as this cytological property is characteristic of MDS.[2,3]

The category MDS/MPN was newly created in the WHO 2001 classification[2] and confirmed in the 2008 classification.[3] It consists of chronic myelomonocytic leukemia, atypical chronic myeloid leukemia (*BCR-ABL1*-negative), juvenile myelomonocytic leukemia, and unclassifiable myelodysplastic/myeloproliferative neoplasms.

Statistical analysis

We investigated relative survival, a measure of the probability of cancer survival after adjustment for competing causes of death, and defined as the ratio of the observed survival of the group of cancer patients of interest to the expected survival of a group of people of the same sex, age, and year of death in the general population.[15,16] Expected survival was estimated from cancer registry-specific population life tables by the Hakulinen method.[17]

The cancer registries provided data on malignancies diagnosed in 1995-2002 with follow up available until 2003; we used the period method[18] to give the most up-to-date estimate of 5-year relative survival for these cases, i.e. the 5-year survival in the period 2000-2002. Using this approach a period of follow up (2000-2002), rather than a period of diagnosis, is selected and survival is estimated from the survival experience of patients followed up to 2000-2002, who were diagnosed in years before 2000.[18] We estimated the 5-year relative survival for each myeloid malignancy grouping, by age at diagnosis and by European region.

To compare survival by European region the data were age-adjusted (direct method) using the same weightings as applied in EUROCARE-4.[14] The analyses were carried out using SEER STAT software, version 6.5.1. (Information Management Services, Inc. and Surveillance Research Program of the Division of Cancer Control and Population Sciences, National Cancer Institute, USA).

Results

Three of the 48 cancer registries participating in HAEMACARE had less than 70% microscopically verified cases, three had over 15% of cases discovered at

Table 1. Cases of myeloid malignancy diagnosed in European adults in 1995-2002, by European region, country and cancer registry, with cancer registry data quality indicators.

European region	Country/Area	Cancer registry	National registration (%)[1]	Cases diagnosed in 1995-2002		
			N. of cases	NOS morphology[2] (%)	DCO[3]/ autopsy[4] (%)	Microscopically verified[4] (%)
Northern Europe						
Iceland	Iceland	100	92	1	0	100
Norway	Norway	100	2,181	14	3	97
Sweden	Sweden	100	7,562	5	1	100
UK and Ireland						
Ireland	Ireland	100	2,810	14	3	96
UK, England	East Anglia	5.4	2,727	3	2	76
	Northern &Yorkshire	13.3	5,312	3	2	90
	Oxford	5.4	1,312	6	0	100
	West Midlands	10.7	4,594	6	9	74
UK, Northern Ireland	Northern Ireland	100	1,259	9	1	47
UK, Scotland	Scotland	100	6,473	3	1	92
UK, Wales	Wales	100	2,059	8	17	57
Central Europe						
Austria	Austria	100	3,355	15	15	82
France	Côte d'Or Hématologique	0.9	584	1	0	100
Germany	Saarland	1.3	892	7	4	92
Switzerland	Basel	6.1	233	2	3	99
	Geneva	5.6	275	8	0	99
	St. Gallen	7.2	299	7	1	100
	Ticino	4.3	125	14	6	94
The Netherlands	Amsterdam	17.6	996	5	0	100
	Eindhoven	6.1	365	3	0	100
	North Netherlands	12.9	844	5	2	100
	Twente	7.2	495	6	1	100
Southern Europe						
Italy	Alto Adige	0.8	203	8	0	98
	Biella	0.3	289	2	0	98
	Ferrara	0.6	323	13	1	97
	Firenze-Prato	2.0	1,386	17	1	65
	Friuli Venezia Giulia	2.1	762	15	3	100
	Genova	1.6	1,121	8	1	75
	Modena	1.1	353	1	0	99
	Napoli	0.9	177	34	1	89
	Parma	0.7	425	19	0	100
	Ragusa	0.5	318	7	1	98
	Reggio Emilia	0.8	294	15	0	92
	Romagna	1.7	774	18	5	95
	Salerno	1.9	422	23	1	98
	Sassari	0.8	258	5	0	100
	Torino	1.6	429	6	2	93
	Trento	0.8	178	20	0	100
	Umbria	1.5	612	11	1	78
	Veneto	3.5	897	26	3	92
Malta	Malta	100	287	2	0	99
Slovenia	Slovenia	100	686	7	1	100
Spain	Girona	1.3	504	11	0	99
Eastern Europe						
Czech Republic	West Bohemia	8.3	610	14	8	85
Poland	Cracow	1.9	236	36	15	80
	Kielce	3.1	352	18	0	92
	Warsaw	4.2	606	15	3	79
Slovakia	Slovakia	100	1,454	20	12	96
Totals			**58,800**	**8**	**4**	**88**

[1]Proportion of national population covered by the cancer registry in 1995-1999; [2]NOS: cases with poorly-specified morphology: those with ICD-O-3 morphology codes 9800, 9801, 9805, and 9860; [3]DCO: cases only discovered from death certificate; [4]Percentages calculated for cases with specified morphology (i.e. excluding cases coded 9800, 9801, 9805, and 9860).

Table 2. Distribution by sex, age at diagnosis and geographic area of patients with myeloid malignancies diagnosed in Europe in the period 1995-2002. Frequencies are given by single ICD-O-3 morphology code and by the groupings proposed in the HAEMACARE study.

HAEMACARE grouping	ICD-O-3 code and description	Cases (N)	Males (%)	Distribution by age (%) 15-49	50-69	70+	Distribution by European region (%) Northern Europe	UK and Ireland	Central Europe	Southern Europe	Eastern Europe
Acute myeloid leukemia (AML)		**18,988**	**53**	**18**	**34**	**48**	**20**	**38**	**13**	**22**	**7**
AML, other	9840 Acute erythroid leukemia 9861 AML, NOS 9867 Acute myelomonocytic leukemia 9870 Acute basophilic leukemia 9872 AML, minimal differentiation 9873 AML, without maturation 9874 AML, with maturation 9891 Acute monocytic leukemia 9910 Acute megakaryoblastic leukemia 9930 Myeloid sarcoma 9931 Acute panmyelosis with myelofibrosis	17,983	53	17	34	49	20	38	13	22	7
AML with recurrent cytogenetic abnormalities	9866 Acute promyelocytic leukemia t(15; 17) (q22; q11-12) 9871 AML with abnormal marrow eosinophils 9896 AML, t(8,21) (q22,q22) 9897 AML, 11q23 abnormalities	685	49	50	34	16	17	40	20	19	4
AML with multilineage dysplasia	9895 AML, with multilineage dysplasia 9984 Refractory anemia with excess blasts in transformation (obsolete)	310	61	5	29	66	25	33	24	15	3
AML, therapy related	9920 Therapy-related AML, NOS 9987 Therapy-related myelodysplastic syndrome, NOS	10	30	20	40	40	0	0	90	10	0
Myeloproliferative neoplasms (MPN)		**17,927**	**51**	**16**	**34**	**50**	**21**	**49**	**8**	**17**	**6**
Chronic myeloid leukemia (CML)	9863 CML, NOS 9875 CML, *BCR/ABL1*-positive	6,794	55	24	33	42	16	31	13	29	11
Other myeloproliferative neoplasms											
Subgroup 1	9740 Mastocytoma, NOS/mast cell sarcoma 9741 Malignant mastocytosis 9742 Mast cell leukemia	66	55	36	35	29	29	15	18	27	11
Subgroup 2	9950 Polycythemia vera 9961 Myelosclerosis with myeloid metaplasia 9962 Essential thrombocythemia 9963 Chronic neutrophilic leukemia 9964 Hypereosinophilia syndrome	7,579	48	13	37	50	26	56	5	11	2
Subgroup 3	9960 Chronic myeloproliferative disease, NOS	3,488	50	8	29	63	19	68	6	5	2
Myelodysplastic syndrome (MDS)	9980 Refractory anemia 9982 Refractory anemia with ring sideroblasts 9983 Refractory anemia with excess blasts 9985 Refractory cytopenia with multilineage dysplasia 9986 Myelodysplastic syndrome 5q-deletion 9989 Myelodysplastic syndrome, NOS	7,982	54	3	21	76	16	66	7	9	2
Myelodysplastic/ myeloproliferative neoplasms (MDS/MPN)	9945 Chronic myelomonocytic leukemia 9876 Atypical CML (*BCR/ABL1*-negative) 9946 Juvenile myelomonocytic leukemia 9975 Myelodysplastic/myeloproliferative neoplasm, unclassifiable	1,672	58	2	22	76	24	47	18	11	1
Myeloid malignancy of unknown type		3,759	52	9	26	65	17	31	7	30	14
Leukemia, NOS	9800 Leukemia, NOS 9801 Acute leukemia, NOS 9805 Acute leukemia, ambiguous lineage	2,747	51	9	25	66	21	35	7	27	11
Myeloid leukemia, NOS	9860 Myeloid leukemia, NOS	1,012	54	9	27	64	7	22	8	40	23
Totals		**50,328**	**52**	**14**	**31**	**55**	**20**	**46**	**10**	**18**	**6**

autopsy or only from the death certificate, and two had over 30% of cases with poorly specified morphology. Patients in these registries (Northern Ireland, Wales, Cracow, Austria, Firenze-Prato and Naples) were excluded from the survival analyses (Table 1). The remaining cancer registries had 50,328 cases: 38% AML, 36% MPN, 16% MDS and 3% MDS/MPN. However, among these there were 2,747 (5.5% of total) cases of leukemia NOS (Table 2) whose morphological descriptions were insufficient to identify them as myeloid malignancies: these cases were also excluded from the analyses.

Table 3 shows the results of the survival analyses as 5-year relative survival for patients followed up in 2000-2002, by subgroup and age (except for subgroups for which the mean number of cases was less than 50).

Five-year relative survival for all myeloid malignancies was 37% (95%CI: 36.1-37.8), but differences between the major categories were large; 5-year relative survival was poorest for AML (17%) and best for MPN (63%). Survival also differed within categories, particularly for AML, where it ranged from 67% for acute promyelocytic leukemia, through 38% for acute pan-myelosis with myelofibrosis, down to 4% for refractory anemia with excess blasts in transformation; for all other subtypes survival was less than 25%.

Survival was more homogeneous among MPN subtypes, although the survival rates of patients with myelosclerosis with myeloid metaplasia and CML were both rather low (35% and 45%, respectively).

For patients with MDS, survival ranged from 12% for those with refractory anemia with excess blasts to 56% for those with refractory anemia with ring sideroblasts. Because of low numbers of MDS/MPN cases it was possible to estimate survival only for cases with chronic myelomonocytic leukemia (19%).

Survival decreased with age in all major disease categories, but particularly for AML and MDS/MPN after the age of 50 years.

Estimates of survival each year after diagnosis are presented in Figure 1A-C. Survival declined markedly during the first year for AML patients but was relatively stable in successive years. Survival after the first year was good for patients with acute promyelocytic leukemia, and remained stable thereafter. For AML with multilineage dysplasia, survival declined persistently from years 2 to 5. For both MPN and MDS, survival declined steadily over the 5 years; the decline was particularly evident for patients with refractory anemia with excess blasts.

Analysis according to European region (Figure 2) showed that 5-year age-adjusted relative survival for patients with AML was fairly homogeneous across Europe, ranging from 11% in Eastern Europe to 16% in Northern and Central Europe. More marked regional differences were evident for patients with acute promyelocytic leukemia, with high survival in Northern Europe (60%) and the UK and Ireland (64%), and poorer survival in Central and Southern Europe (55%).

Regional differences in survival were also marked for patients with MPN, ranging from 74% in Northern Europe to 27% in Eastern Europe. Survival was better in Northern Europe and worse in Eastern Europe for all MPN subtypes except MPN NOS. For CML, the 5-year survival rates were 46% in Northern Europe, 40% in the UK and Ireland, 42% in Southern Europe, 44% in Central Europe, and 17% in Eastern Europe.

Discussion

After reporting previously on the incidence of myeloid malignancies across Europe in 2000-2002,[12] we now report on relative survival for these diseases, analyzing data from 42 cancer registries in 17 European countries. In the previous study[12] we also investigated the completeness of the HAEMACARE database, comparing incidence data obtained from the HAEMACARE database with those published in Cancer Incidence in Five Continents (CI5) which can be considered the gold standard for cancer registration. We found similar incidence rates to those in CI5, indicating that HAEMACARE data are as complete as those of CI5.

In spite of unavoidable bias due to variation in registration quality and coding practices, over 90% of cases (more than 50,000 patients) had adequate morphology specification and were used to estimate survival. To our knowledge this is the largest European dataset used to analyze survival of patients with myeloid malignancies, making it possible to assess and compare survival across the continent not only for common but also for relatively rare entities.

Europeans diagnosed with a myeloid malignancy generally have poor 5-year relative survival.[19] Nevertheless survival varied markedly with subtype, being around 15% in patients with AML but above 60% in those with MPN.

AML is a long-established entity so comparisons of survival over time are possible. In Europe, the 5-year relative survival rate improved from 10% in patients diagnosed in 1985-1989 to 14% in those diagnosed in 1995-1999,[19,20] with no further improvement up to 2000-2002.[21] For US patients diagnosed with AML over the period 1999-2005, the 5-year relative survival was higher at 23%.[22]

Survival of patients with AML with cytogenetic abnormalities was fairly good mainly because its common subtype – acute promyelocytic leukemia – can be effectively treated with all-trans retinoic acid.[23,24] Patients with other subtypes of AML with cytogenetic abnormalities also have good prognoses.[25,26] Our finding that patients with AML with multilineage dysplasia had the worst relative survival is in accord with clinical data.[27,28]

Variation in survival for AML as a whole was fairly contained across Europe, although patients did somewhat better in Northern and Central Europe than in Eastern Europe and the UK and Ireland. Variation in the survival of patients with acute promyelocytic leukemia was not statistically significant given the limited number of cases. This entity is treated effectively by a cheap vitamin A derivative (all-trans retinoic acid)[24]. Note, however, that population-based studies do not normally have access to information on treatment. The interpretation of inter-country differences in AML survival is further complicated by the high percentage of AML NOS cases. These cases may include poor prognosis patients and elderly who undergo less intensive diagnostic work-up than better prognosis and younger patients. An additional reason for the large proportion of AML, NOS is probably that our study protocol required morphologies coded according to ICD-O-3 codes. Cases diagnosed before the adoption of ICD-O-3 (year 2000 by most registries) were coded according to ICD-O-1 or ICD-O-2. These codes were converted into ICD-O-3 using IARC and EUROCARE rules. Cases not classifiable into exact ICD-O-3 entities were classified as AML NOS.

The availability and quality of morphology data varied between cancer registries and countries and, although the analysis was restricted to cancer registries with less than 30% NOS cases, the numbers of cases with poorly defined morphology were relatively high, pointing to the need for the registries to obtain better quality information. Centralized review of slides would have decreased the proportion of NOS cases and improved the quality of our data, but the resources were not available for such a task.

Literature data on the survival of patients with MPN are scarce, except for those with the CML subtype.[6,29] We found that for most of MPN subtypes survival in Europe was good, particularly for patients with polycythemia vera and essential thrombocythemia, as reported in population-based and clinical studies.[29-32]

CML has been correctly archived by cancer registries since the 1970s, in coincidence with identification of the causal t(9;22)(q34;q11) chromosome transition. Survival improved from 37% in Europe in 1990-1994,[5] to 45% in the present study (Table 3). The introduction of tyrosine kinase inhibitors to treat CML early in the new millennium may have been partly responsible for this improvement. These drugs are now first-line treatments for CML.[33] No information on the use of tyrosine kinase inhibitors was available for the present study and it is possible that the dissemination of these treatments will result in a further improvement in CML survival in the years beyond those of the present study.

The survival of European patients with CML was similar to that of US SEER patients diagnosed in 1984-1993.[34]

Table 3. Period estimates of 5-year relative survival (RS %) with 95% confidence intervals (CI) for European patients with myeloid malignancies alive in 2000-2002. RS is only shown for malignancies with a mean number of cases (Mean N) >50.

HAEMACARE grouping	ICD-O-3 code and description	All ages (15-99)			Age 15-49		Age 50-69		Age 70+	
		Mean N[1]	RS (%)	95% CI	RS (%)	95% CI	RS (%)	95% CI	RS (%)	95% CI
Acute myeloid leukemia (AML)[2]		7,111	17.0	(16.1-18.0)	47.4	(44.6-50.1)	15.4	(13.9-17.0)	2.7	(2.1-3.4)
AML, other[2]		6,716	15.1	(14.2-16.1)	43.6	(40.7-46.5)	14.0	(12.5-15.5)	2.5	(1.9-3.2)
	9840 Acute erythroid leukemia	131	8.6	(4.4-14.5)	34.4	(15.5-54.2)	3.9	(0.7-12.3)	2.4	(0.3-8.9)
	9861 AML, NOS	5,580	13.9	(12.9-14.9)	42.6	(39.3-45.8)	12.6	(11.1-14.2)	1.9	(1.4-2.6)
	9867 Acute myelomonocytic leukemia	416	23.6	(19.0-28.6)	52.6	(41.1-63.0)	24.9	(17.6-32.9)	2.6	(0.7-7.0)
	9873 AML, without maturation	51	23.1	(12.3-35.8)	-	-	-	-	-	-
	9874 AML, with maturation	101	17.9	(10.4-27.1)	-	-	24.1	(12.0-38.5)	-	-
	9891 Acute monocytic leukemia	297	18.6	(13.7-24.2)	49.6	(35.5-62.3)	12.3	(6.3-20.3)	3.9	(0.9-10.8)
	9931 Acute pan-myelosis with myelofibrosis	88	37.5	(26.1-48.8)	-	-	37.6	(21.7-53.5)	33.1	(16.7-50.4)
AML, with recurrent cytogenetic abnormalities[2]		269	64.1	(57.5-69.9)	78.2	(70.2-84.3)	59.7	(48.3-69.4)	13.5	(4.5-27.6)
	9866 Acute promyelocytic leukemia t(15; 17) (q22; q11-12)	258	66.8	(60.0-72.8)	79.2	(71.1-85.3)	64.4	(52.0-74.4)	12.1	(3.6-26.2)
AML with multilineage dysplasia[2]		124	4.0	(1.2-9.8)	-	-	6.0	(1.1-17.1)	-	-
	9984 Refractory anemia with excess blasts in transformation (obsolete)	108	4.4	(1.2-10.7)	-	-	6.8	(1.2-19.5)	-	-
Myeloproliferative neoplasms (MPN)[2]		6,614	63.4	(61.8-64.9)	79.0	(76.3-81.4)	67.1	(64.9-69.2)	52.1	(49.6-54.6)
Chronic myeloid leukemia (CML)[2]		2,426	44.9	(42.6-47.3)	66.6	(62.5-70.3)	48.6	(44.8-52.2)	22.5	(19.3-25.8)
	9863 CML, NOS	2,399	44.6	(42.3-47.0)	66.4	(62.3-70.2)	48.3	(44.6-52.0)	22.3	(19.1-25.6)
Other myeloproliferative neoplasms										
Subgroup 2[2]		2,844	82.3	(80.0-84.3)	96.0	(92.9-97.7)	83.2	(80.2-85.8)	76.6	(72.5-80.2)
	9950 Polycythemia vera	1,382	84.8	(81.5-87.5)	94.9	(89.7-97.5)	86.4	(82.3-89.6)	79.4	(73.1-84.4)
	9961 Myelosclerosis with myeloid metaplasia	249	34.6	(27.6-41.6)	-	-	33.9	(23.6-44.5)	29.8	(20.7-39.5)
	9962 Essential thrombocythemia	1,230	89.9	(86.2-92.7)	98.9	(92.0-99.9)	90.4	(85.5-93.7)	85.8	(78.7-90.7)
Subgroup 3	9960 Chronic myeloproliferative disease, NOS	1,311	55.3	(51.5-58.9)	89.2	(81.3-93.9)	62.8	(57.1-68.0)	42.5	(37.5-47.5)
Myelodysplastic syndrome (MDS)[2]		3,077	30.8	(28.8-32.8)	51.8	(42.0-60.7)	36.5	(32.7-40.3)	27.2	(24.8-29.7)
	9980 Refractory anemia	462	49.0	(42.7-55.0)	-	-	52.3	(42.2-61.4)	43.9	(35.7-51.8)
	9982 Refractory anemia with ring sideroblasts	251	56.1	(47.1-64.2)	-	-	68.9	(52.4-80.7)	51.1	(40.2-60.9)
	9983 Refractory anemia with excess blasts	361	11.5	(7.5-16.5)	-	-	9.0	(4.0-16.6)	12.2	(7.0-19.0)
	9989 Myelodysplastic syndrome, NOS	2,019	27.1	(24.7-29.5)	47.3	(35.1-58.5)	35.0	(30.2-39.8)	23.2	(20.5-25.9)
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)[2]		650	19.6	(16.1-23.4)	73.5	(42.5-89.5)	24.8	(17.7-32.4)	16.6	(12.8-20.9)
	9945 Chronic myelomonocytic leukemia	646	19.3	(15.7-23.0)	-	-	24.0	(17.0-31.6)	16.7	(12.8-21.0)
All myeloid malignancies[3]		17,346	37.0	(36.1-37.8)	61.7	(59.7-63.6)	39.4	(38.1-40.8)	26.2	(25.0-27.3)

[1]Mean number of cases contributing to period estimates of 5-year survival for 2000-2002; [2]ICD-O-3 codes as reported in Table 2; [3]Excluding leukemia, NOS (as defined in Table 2) since insufficient information was available to be sure that the disease was of myeloid lineage. - Insufficient cases to estimate 5-year relative survival.

However, in more recent SEER cohorts[22] (1999-2005), the 5-year relative survival of patients with CML was 53%. Thus, survival in Europe for CML lags well behind that in the USA. Furthermore, European patients were characterized by marked survival variation for this highly treatable malignancy, with poor outcomes in Eastern Europe.

Population-based studies on MDS and MDS/MPN from specialized European[6,35,36] and USA registries[37] are generally carried out on a small-scale, whereas the present analysis was based on over 10,000 European cases. The MDS/MPN category is dominated by chronic myelomonocytic leukemia which is associated with a worse survival than MDS (this being one of the reasons why it was separated from MDS).[37] A large USA study[29] estimated the 3-year relative survival to be 21% for myelomonocytic leukemia and 45% for MDS, consistent with European findings (Table 3). As suggested previously[12] it is likely that MDS and MDS/MPN were underre-

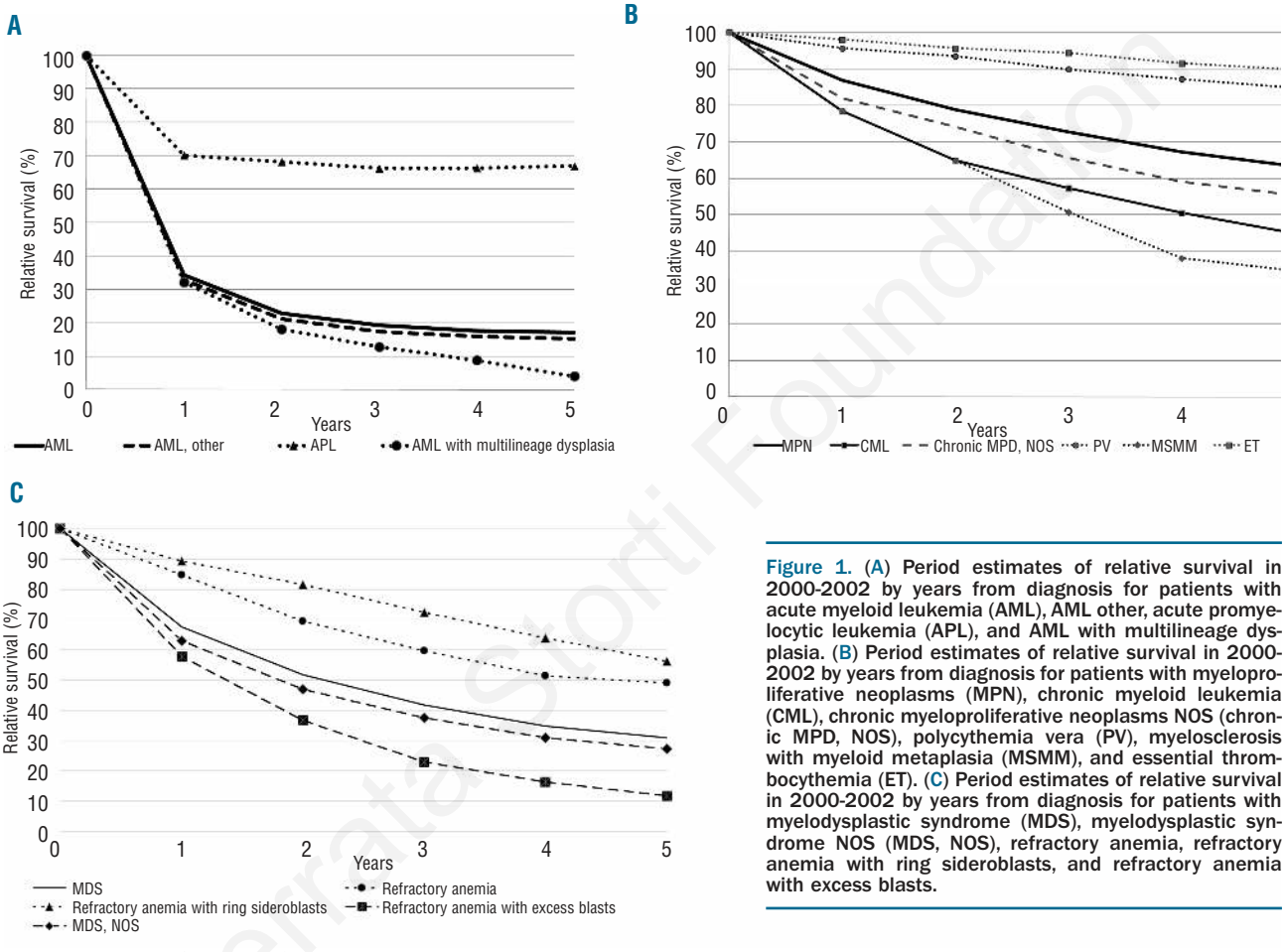

Figure 1. (A) Period estimates of relative survival in 2000-2002 by years from diagnosis for patients with acute myeloid leukemia (AML), AML other, acute promyelocytic leukemia (APL), and AML with multilineage dysplasia. (B) Period estimates of relative survival in 2000-2002 by years from diagnosis for patients with myeloproliferative neoplasms (MPN), chronic myeloid leukemia (CML), chronic myeloproliferative neoplasms NOS (chronic MPD, NOS), polycythemia vera (PV), myelosclerosis with myeloid metaplasia (MSMM), and essential thrombocythemia (ET). (C) Period estimates of relative survival in 2000-2002 by years from diagnosis for patients with myelodysplastic syndrome (MDS), myelodysplastic syndrome NOS (MDS, NOS), refractory anemia, refractory anemia with ring sideroblasts, and refractory anemia with excess blasts.

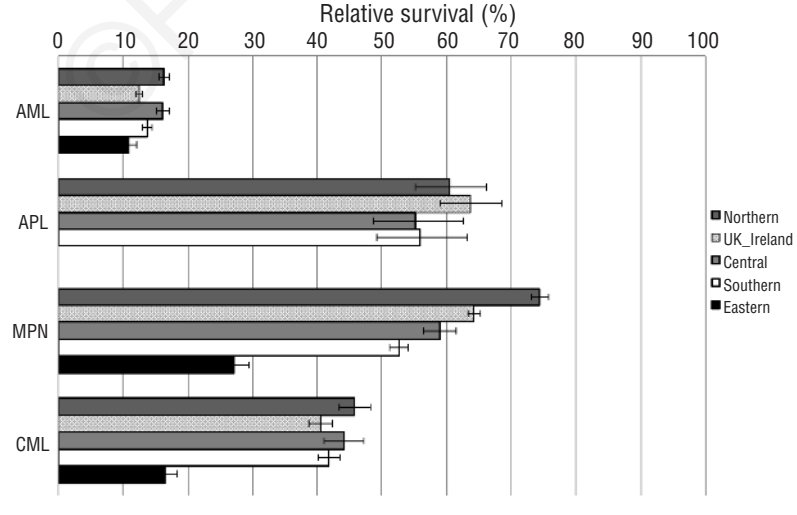

Figure 2. Age-adjusted period estimates in 2000-2002 of 5-year relative survival for patients with acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), myeloproliferative neoplasm (MPN) and chronic myeloid leukemia (CML), by European region.

ported in the present study as they were considered non-malignant and hence not registered by most European cancer registries until the adoption of the ICD-O-3. Treatment for MDS remained static until relatively recently when drugs such as lenalidomide, azacytidine and decitabine were introduced with encouraging results.[39-42] However any population-based effect on survival of patients with MDS will not be evident for several years.

We found that the survival decreased markedly with age for all myeloid malignancies, with a steeper decrease than reported for most other cancers.[5] In general this decline is attributed to less rigorous application of treatment protocols in older patients, in part because they often have co-morbidities. Few clinical trials are conducted specifically on older patients.[43]

To conclude, this is the first paper to present large-scale European survival data for patients with myeloid malignancies using prognosis-based groupings of entities defined by the ICD-O-3/WHO classifications. We documented poor survival for Europeans diagnosed with AML and MDS/MPN compared to those with MDS and CML. We also identified differences in AML subtypes, with good survival for patients with acute promyelocytic leukemia and poor survival for those with AML with multilineage dysplasia. Poor survival in some parts of Europe, particularly for treatable diseases such as CML, is of concern to hematologists and public health authorities.

Appendix: HAEMACARE Working Group

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