The incidence and outcome of myeloid malignancies in 2,112 adult patients in South East-England

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There is a paucity of epidemiological data on chronic myeloproliferative disorders and myelodysplastic syndromes (MDS), while subtypes of acute myeloid leukemia (AML) are rarely defined. We identified 2,112 adult myeloid malignancies in the South Thames area between 1999 and 2000. The incidence (European standard population) of AML was 3.00/100,000, that of MDS 3.47/100,000, chronic myelomonocytic leukemia (CMML) 0.46/100,000, idiopathic myelofibrosis (IMF) 0.37/100,000, polycythemia vera (PV) 1.08/100,000, primary thrombocythemia (PT) 1.65/100,000 and chronic myeloid leukemia (CML) 1.09/100,000. The 3-year survival for AML was 15%, MDS 45%, CMML 29%, IMF 48%, PV 80%, PT 81% and CML 50% We believe this study reflects the true incidence and outcome of myeloid malignancies in South East England.

Key words: myeloid malignancies, incidence, survival.

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The 2001 World Health Organization[1] (WHO) re-classification of acute myeloid leukemia (AML) included myelodysplastic syndrome (MDS), chronic myeloproliferative disease (CMPD) and the myelodysplastic/myeloproliferative (MDS/MPD) clonal hematopoietic stem cell diseases. The features of MDS/MPD overlap with those of MDS and CMPD, and chronic myelomonocytic leukemia (CMML) was re-classified into MDS/MPD by the WHO (ICD-03 code M9945/3). Because MDS and CMPD were not considered to be neoplastic, cancer registries rarely collected data on these disorders and therefore information on the incidence of MDS and CMPD in the population is limited.[2-4] In the present study, we describe the incidence and survival of patients aged 16 years or greater with myeloid malignancies in South Thames.

Design and Methods

The study population was 5,499,841 (Office of National Statistics, 2001 census figures, published April 2001) including patients aged 16 years or greater diagnosed with myeloid malignancies between 1999 and 2000 in a total of 231 health care institutions. The method of data collection has been previously described.[5] Between January 1999 and December 2000 patients with myeloid malignancies were identified and classified into four diagnostic groups: i) AML ii) MDS, iii) CMML and iv) CMPD. The French, American and British (FAB) classification[6,7] was used to subclassify AML and MDS. CMPD were defined using the Medical Research Council, Primary Thrombocythemia protocol and established diagnostic criteria for polycythemia vera (PV), idiopathic myelofibrosis (IMF)[8] and chronic myeloid leukemia (CML).[9] Bi-annually hematologists validated their cases and additional myeloid malignancies, seen outside of hematology departments, or the residential area, were captured by the Thames Cancer Registry. Deaths from myeloid malignancies were identified by the Office of National Statistics.

Statistical methods

Age- and sex-specific incidence rates were calculated using population estimates from the 2001 UK population census, the European standard population (ESP) and the World standard population (WSP). The methodology described by Jensen *et al.*[10] was used to test for statistical significance of the standardized rate ratio. The dates of diagnosis and death or the close of study (05th December 2002) were used to estimate survival by the Kaplan–Meier method. Survival was compared by gender and between patients aged <65 years and ≥65 years. Survival comparisons between groups were made using the log rank test. p values of <0.05 was considered to be statistically significant. Statistical analyses were performed using STATA™ version 8.

Results and Discussion

Age and sex standardized incidence rates

A total of 2,112 myeloid malignancies were identified between 1999 and 2000. Table 1

illustrates the distribution of the 826 cases of CMPD identified. The incidence of IMF was 0.37/10,000 ESP, the median age 69 years (range 37-93 years) with 39% of patients aged <65 years. The median age of patients with PV and PT was 72 (range 33-95) and 73 years (range 21-99), respectively. There were no significant differences by gender for either disorder; the male to female ratio was 1.11 (0.73-1.69) and 0.76 (95% CI 0.54-1.06), respectively. The ESP and WSP incidence rates for PV were 1.08/100,000 and 0.74/100,000, respectively and for PT 1.65/100,000 and 1.13/100,000 respectively. There were 180 CML cases giving an overall incidence rate of 1.09/100,000, ESP (Table 2). Fifty-one percent of these patients were aged <65 years, and the median age was 65 years (range 20-98 years). Six hundred and eighty cases of MDS, defined by the FAB criteria, were registered (Table 1). The median age at presentation for MDS (excluding CMML) was 77 years (range 24-98 years). There was a significant male predominance; the male to female ratio being 1.62 (95% CI 1.30-2.02). The overall age-standardized incidence rate was 3.47/ 100,000, ESP (Table 2).

There were 507 cases of AML (4% M0, 12% M1, 12% M2, 6% M3/M3v, 10% M4/M4Eo, 7% M5a/M5b, 3% M6, 0.4% M7 and 46% unclassified) (Table 1). The median age of patients at diagnosis of AML was 71 years (range 16-98 years), 52% were aged ≥65 years and 16% were aged <44 years. The incidence rate in men was 3.71/100,000 ESP and that in women 2.42 /100,000 ESP (Table 2). Ninety-nine cases of CMML were identified (Table 1); the majority (93%) of these patients were aged ≥65 years and the median age of 78 years (range 45-98 years). The incidence rate was 0.46/100,000 (ESP) and the male to female ratio 2.09 (95% CI 1.17-3.72).

Table 1. Registrations of myeloid malignancies in South Thames, 1999-2000.

	Total cases n.	*%*
Chronic myeloproliferative diseases (CMPD)		
Idiopathic myelofibrosis	61	7
Polycythemia vera (PV)	185	22
Myelofibrotic transformation of PV	4	0.5
Primary thrombocythemia (PT)	297	36
Myelofibrotic transformation of PT	10	9
CMPD, unspecified	78	1
CMPD, other	11	22
Chronic myeloid leukemia	180	–
	826	**100**
Myelodysplastic syndromes (MDS)		
Refractory anemia	274	40
RA with ringed sideroblasts	72	11
RA with excess blasts	100	15
RA with excess blasts in transformation	51	8
MDS, unspecified	172	25
MDS, other	11	2
	680	**100**
Acute myeloid leukemia (AML)		
AML, M0	18	4
AML, M1	63	12
AML, M2	63	12
AML, M3	26	5
AML, M3v	3	1
AML, M4	45	9
AML, M4Eo	4	1
AML, 5a	24	5
AML, 5b	9	2
AML, M6	16	3
AML, M7	2	0.4
AML, other	2	0.4
AML, unspecified	232	46
	507	**10**
Chronic myelomonocytic leukemia	**99**	**100**
Total myeloid malignancies registered	**2,112**	

Survival

One hundred and sixteen patients whose registration was based only on death certification or who survived less than 1 day were not evaluated for survival. Among the CMPD the median survival for IMF was 33 months (95% CI 15-45), whereas the median survival for PV and PT was not reached. The estimated 3-year survival for these latter two disorders was 80% (95% CI 73-86) and 81% (95% CI 76-85), respectively. For all myeloproliferative disorders there was a significant difference ($p<0.05$) in survival between patients aged <65 years and those aged ≥65 years but no differences in survival by gender (Table 3). The median survival for CML was not reached at 45 months and 3-year survival was 50% (95% CI 41-58). There was a significant difference in 3-year survival between patients aged <65 and ≥65 years (74% vs. 17%, $p<0.001$), but no difference ($p=0.397$) between sexes. The median survival of patients with any subtype of MDS (subtypes combined) was 32 months (95% CI 26-35) but survival varied according to subtype refractory anemia [RA] 39 months (95% CI 34-45), RA with ringed sideroblasts [RARS] not reached at 45 months, RA with excess blasts [RAEB] 14 months (95% CI 9-26) and RAEB in transformation [RAEBt] 7 months (95% CI 3-18). Table 3 shows that survival was significantly different for patients aged <65 years or ≥65 years with RA and RAEBt ($p=0.05$), and for females with RA versus males with RA ($p=0.008$). The median survival of patients with AML was 5 months (95% CI 4 - 7) ad 3-year estimated survival was 15% (95% CI 12-19). Three-year survival among patients aged ≥65 years was 2% (95% CI 0.5-5) compared to 37% among patients <65 years ($p<0.001$). There was no difference in survival by sex ($p=0.358$). Table 3 shows 3-year survival by FAB classifications for AML; the range was from 12% (M6) to 48% (M3).

The median survival of patients with CMML was 14 months (95% CI 9-20) with no difference in survival according to either the patients' age ($p=0.670$) or gender ($p=0.353$) (Table 3).

Table 2. Age- and sex-standardized incidence rates (per 100,000) for myeloid malignancies in South Thames, 1999-2000.

	IMF	*PV*	*CMPDs PT*	*CML*	*RA*	*MDS RARS*	*RAEB*	*RAEBt*	*MDS, all subtypes*	*AML, all subtypes*	*CMML*
Age (years)											
Median age	69	72	73	65	78	77	77	77	77	71	78
(range)	(37-93)	(33-95)	(21-99)	(20-98)	(37-98)	(27-97)	(27-96)	(35-97)	(24-98)	(16-98)	(45-98)
<65 years (%)	39	31	31	51	14	15	15	27	17	48	7
Age-specific incidence rates											
16-24	0	0	0.07	0.28	0	0	0	0.07	0.07	1.34	0
25-34	0	0.05	0.37	1.01	0	0	0.09	0.05	0.41	1.24	0
35-44	0.05	0.34	1.26	0.82	0.24	0.05	0.14	0.05	0.72	1.59	0
45-54	0.34	1.07	1.3	1.35	0.73	0	0.28	0.17	1.86	2.2	0.28
55-64	1.26	2.22	2.52	1.78	1.41	0.74	0.37	0.59	4.44	5.41	0.15
65-74	1.27	5.24	6.51	2.8	7.14	1.81	2.44	1.63	16.45	11.66	2.35
75-84	2.18	7.43	12.82	4.49	13.59	3.59	4.61	2.05	31.41	16.66	5.77
85+	2.02	4.04	11.1	7.74	17.5	4.37	7.4	1.01	45.43	19.18	7.07
Males	0.8	1.7	2.38	2.06	3.79	1.06	1.85	0.72	10.02	6.24	1.51
Females	0.46	1.68	3.13	1.39	2.09	0.55	0.57	0.33	5.01	3.89	0.69
Standardized incidence rates											
European Standard Population (ESP)											
Males	0.43	1.13	1.39	1.34	1.75	0.46	0.8	0.4	4.56	3.71	0.67
Females	0.33	1.01	1.85	0.87	1.14	0.32	0.3	0.23	2.81	2.42	0.32
All persons	0.37	1.08	1.65	1.09	1.37	0.37	0.5	0.3	3.47	3.00	0.46
M:F ratio	1.3	1.11	0.76	0.75	1.53	1.43	2.66	1.73	1.62	1.53	2.09
95% CI	(0.64-2.61)	(0.73-1.69)	(0.54-1.06)	(0.53-1.05)	(1.08-2.16)	(0.74-2.75)	(1.46-4.86)	(0.79-3.78)	(1.30-2.02)	(1.18-1.98)	(1.17-3.72)
World Standard Population (WSP)											
Males	0.28	0.79	0.97	1	1.07	0.28	0.5	0.26	2.83	2.65	0.41
Females	0.23	0.68	1.27	0.67	0.75	0.21	0.2	0.17	1.87	1.83	0.19
All persons	0.25	0.74	1.13	0.83	0.85	0.23	0.32	0.21	2.24	2.2	0.28
UK studies reporting epidemiological data on myeloid malignancies											
Leukaemia Research Fund (LRF) Centre[11]											
Males (WSP)	0.29	0.53	0.33	0.72	0.73	0.25	0.46	–	1.71	1.94	0.27
Females (WSP)	0.16	0.35	0.4	0.47	0.54	0.15	0.23	–	1.06	1.51	0.14
The Oxford Cancer Intelligence Unit[2]											
Males (ESR)	–	1.2	1.2	1	–	–	–	–	2.9	3.9	–
Females (ESR)	–	0.8	1.1	0.6	–	–	–	–	1.3	2.6	–
All persons (ESR)	–	1	1.2	0.8	–	–	–	–	1.9	3.2	–

– not reported

A lack of published population data may bias incidence and survival analyses and flaw healthcare planning. Previous incidence data for AML[2] vary from those reported in the South Thames and three studies have reported a lower incidence of MDS.[2,11,12] These differences may be explained in part by the exclusion of pediatric cases and increased reporting of elderly patients in our study. One study classified RAEBt in AML and CMML with CML or MDS,[2] a further study only identified patients from bone marrow smears[12] and the third was a specialist register and therefore not a true population study.[11]

The discovery of JAK-2 mutation,[13] will improve the diagnosis and calculation of the true incidence of CMPD in the future. The incidence of PT in this study is higher than that in two other population studies[2,4] whereas the incidence of PV is comparable to that in the Oxford Cancer Intelligence Unit but lower than in a Swedish study (ESP of 2.02 per 100,000).[4] Data for IMF in the UK are scant but we report a similar incidence to that in the Swedish study (0.31 per 100,000).[4] Clinical trials have previously focused on intensive treatment regimens which bias patients' entry and data collected in such trials may, therefore, not be generalizable to a population in which the median age of patients is >70 years. Colman *et al.*[14] reported a 1-year crude population survival rate for AML in England and Wales between 1971 and 1995 of 23%. Over the period 1999-2000 our study showed no difference in survival to that reported by Coleman *et al.* or that found in the Eurocare population study covering the same period.[15] In our study, the median survival for patients aged ≥65years was poor, being only 2 months, and comparable to that in population studies from the USA[16] and UK.[17] Cancer registries have historically not collected data for AML by sub-classification making survival comparisons difficult. However, the Northern Leukaemia Register[17] showed survival for patients with AML M3 to be similar at 46 months; differ-

Table 3A. Median, 1-year and 3-year survival for patients with myeloid malignancies in South Thames.

	Median survival (months)	One-year survival % (95% CI)	Three-year survival % (95% CI)	Log rank test p value
Chronic myeloproliferative diseases (CMPD)				
IMF	33	72 (60-83)	48 (34-61)	
<65 years	not reached	82 (63-93)	66 (41-82)	
≥65 years	23	65 (48-78)	37 (22-53)	0.021
Males	33	72 (54-85)	43 (25-60)	
Females	25	71 (50-84)	54 (33-71)	0.449
PV not reached	90 (84-94)	80 (73-86)		
<65 years	not reached	98 (87-99)	90 (78-95)	
≥65 years	not reached	87 (79-82)	76 (66-83)	0.015
Males	not reached	91 (82-96)	81 (73-90)	
Females	not reached	95 (88-95)	82 (71-89)	0.812
PT not reached	93 (89-95)	81 (76-85)		
<65 years	not reached	97 (91-99)	94 (86-97)	
≥65 years	not reached	91 (84-95)	75 (64-82)	0.002
Males	not reached	89 (81-93)	78 (68-85)	
Females	not reached	95 (91-97)	83 (76-88)	0.228
CML	not reached	73 (65-69)	50 (41-58)	
<65 years	not reached	90 (81-95)	74 (64-82)	
≥65 years	13	51 (38-62)	17 (8-29)	<0.001
Males	not reached	75 (65-83)	52 (41-63)	
Females	27.5	72 (59-89)	46 (33-58)	0.397
Myelodysplastic syndromes (CMML are excluded)				
RA	39	76 (70-80)	54 (47-60)	
<65 years	not reached	84 (67-93)	69 (51-82)	
≥65 years	37	74 (68-80)	52 (44-58)	0.050
Males	33	71 (63-78)	44 (35-53)	
Females	45	80 (72-86)	65 (56-73)	0.008
RARS	not reached	77 (65-85)	58 (45-69)	
<65 years	not reached	82 (44-95)	72 (37-90)	
≥65 years	38	76 (63-85)	54 (40-67)	0.283
Males	38	78 (62-88)	60 (42-74)	
Females	not reached	75 (57-87)	55 (36-71)	0.811
RAEB	14	53 (43-62)	21 (13-32)	
<65 years	35	76 (44-91)	43 (15-68)	
≥65 years	11	50 (38-60)	18 (9-28)	0.073
Males	14	54 (42-65)	19 (9-31)	
Females	13	51 (33-67)	29 (13-46)	0.086
RAEBt	7	39 (25-52)	29 (17-42)	
<65 years	20	69 (37-87)	46 (19-69)	
≥65 years	5.1	28 (14-43)	0	0.055
Males	7	40 (22-57)	26 (12-43)	
Females	5	38 (17-59)	33 (13-54)	0.853
MDS, NOS	30	66 (57-72)	44 (36-52)	
<65 years	not reached	91 (76-97)	46 (57-87)	
≥65 years	17	58 (44-68)	35 (26-44)	<0.001
Males	21	62 (50-72)	40 (28-52)	
Females	33	38 (57-78)	48 (36-59)	0.185
MDS (all subtypes)	32	67 (63-71)	45 (41-49)	
<65 years	not reached	82 (73-88)	66 (56-74)	
≥65 years	27	64 (60-68)	40 (36-45)	<0.001
Males	27	65 (64-70)	39 (33-44)	
Females	39	71 (65-76)	53 (47-49)	0.002

Table 3B. Median, 1-year and 3-year survival for myeloid malignancies in South Thames.

	Median survival (months)	One-year survival % (95% CI)	Three-year survival % (95% CI)	Log rank test p value
Acute myeloid leukemia				
AML	5	32 (27-36)	15 (12-19)	
<65 years	19	61 (53-68)	37 (29-44)	
>65 years	3	15 (11-19)	2 (0.5-5)	<0.001
Males	7	33 (27-39)	15 (10-20)	0.358
Females	5			
AML, M0	4	17 (44-38)	0	
AML, M1	9	38 (26-50)	17(9-29)	
AML, M2	6	40 (28-52)	25 (16-37)	
AML, M3/M3v	17	55 (35-71)	48 (28-65)	
AML, M4	7	34 (22-48)	17 (8-29)	
AML, M5	4	32 (16-48)	19 (7-34)	
AML, M6	5	31 (11-63)	12 (2-32)	
AML, M7	1	0	0	
AML, unspecified	5	28 (22-35)	11 (6-13)	
Chronic myelomonocytic leukemia				
CMML	14	52 (42-62)	29 (20-39)	
<65 years	14	60 (12-88)	20 (8-58)	
≥65 years	14	52 (42-62)	31 (21-41)	0.670
Males	14	55 (45-65)	32 (23-42)	
Females	13	54 (40-66)	25 (14-37)	0.353

ences in survival were reported with other FAB types in patients aged less than 55 years (*data not shown*). The comparison of survival of patients with MDS is difficult due to a lack of published data. UK Guidelines for myelodysplastic syndromes[18] report survival data from clinical trials ranging from 0.3 years to 11.8 years in patients <60 years old to 0.5 to 4.8 years in those ≥60 years old. In our series, the median survival of patients aged <65 years was not reached at 46 months and their 3-year survival was 66% whilst median survival in patients aged ≥65 years was 27 months and three year survival was 40%. Maynadie *et al.*[3] reported corrected 5-year survival rates of 33% in an unselected French population with MDS compared to the 3-year survival of 45% reported in this series. The median survival for CMML of 14 months (95% CI)[19-20] and 3-year survival of 29% in our series is comparable to the rates in other international studies that identified CMML separately from CML and MDS.[3,19] Our study provides survival data for CPMD in the UK for the first time with comparable outcomes for patients with PT,[20] IMF[20] and CML.[17]

We believe this study provides a benchmark in the UK for incidence rates and survival in all patients with subtypes of myeloid malignancies.

All authors contributed equally to the writing and conception of the manuscript.

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