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Myeloid malignancies in the real-world: Occurrence, progression and survival in the UK's population-based Haematological Malignancy Research Network 2004–15

Eve Roman[a,*], Alex Smith[a], Simon Appleton[a], Simon Crouch[a], Richard Kelly[b], Sally Kinsey[c], Catherine Cargo[b], Russell Patmore[d]

[a] Epidemiology and Cancer Statistics Group, Department of Health Sciences, University of York, YO10 5DD, UK
[b] St. James's Institute of Oncology, Leeds Teaching Hospitals NHS Trust, LS9 7TF, UK
[c] Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, LS1 3EX, UK
[d] Queens Centre for Oncology, Castle Hill Hospital, HU16 5JQ, UK

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ABSTRACT

Background: Population-based information on cancer incidence, prevalence and outcome are required to inform clinical practice and research; but contemporary data are lacking for many myeloid malignancy subtypes.
Methods: Set within a socio-demographically representative UK population of ~4 million, myeloid malignancy data (N = 5231 diagnoses) are from an established patient cohort. Information on incidence, survival (relative & overall), transformation/progression, and prevalence is presented for >20 subtypes.
Results: The median diagnostic age was 72.4 years (InterQuartile Range 61.6–80.2), but there was considerable subtype heterogeneity, particularly among the acute myeloid leukaemias (AML) where medians ranged from 20.3 (IQR 13.9–43.8) for AML 11q23 through to 73.7 (IQR 57.3–79.1) for AML with no recurrent genetic changes. Five-year Relative Survival (RS) estimates varied hugely; from <5% for aggressive entities like therapy-related AML (2.6%, 95% Confidence Interval 0.4–9.0) to >85% for indolent/treatable conditions like chronic myeloid leukaemia (89.8%, 95% CI 84.0–93.6). With a couple of notable exceptions, males experienced higher rates and worse survival than females: the age-standardized incidence rates of several conditions was 2–4 higher in males than females, and the 5-year RS for all subtypes combined was 48.8% (95% CI 46.5–51.2) and 60.4% (95% CI 57.7–62.9) for males and females respectively. During follow-up (potential minimum 2 years and maximum 11 years) myelodysplastic syndrome (MDS) progression to AML ranged from 25% for refractory anaemia with excess blasts through to 5% for refractory anaemia with ring sideroblasts: the median interval between MDS and AML diagnosis was 9.0 months (IQR 4.8–17.4 months).
Conclusions: The marked incidence and outcome variations seen by subtype, sex and age, confirm the requirement for "real-world" longitudinal data to inform aetiological hypotheses, healthcare planning, and future monitoring of therapeutic change. Several challenges for routine cancer registration were identified, including the need to link more effectively to diagnostic and clinical data sources, and to review policies on the recording of progressions and transformations.

1. Introduction

Accounting for around a third of all newly diagnosed haematological malignancies, myeloid neoplasms (acute myeloid leukaemias, myelodysplastic syndromes, and myeloproliferative neoplasms) comprise a complex group of cancers with diverse aetiologies, treatment pathways and outcomes [1,2]. Contemporary population-based information about the occurrence and outcome for many of these malignancies is however sparse, and for some of the rarer cancer entities included within these categories is largely non-existent. This absence of relevant data reflects the paradigm changing nature of the new classification systems implemented over the last 15 years; the 2001 World Health Organization (WHO) schema for tumours of the haematopoietic and lymphoid tissue incorporating, for the first time, genetic data with information on morphology, immunology and clinical

* Corresponding author.
E-mail address: eve.roman@york.ac.uk (E. Roman).

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parameters [3]. This not only resulted in significant refinements to previously defined categories, but also to the addition of several new malignancies including, for example, the myelodysplastic syndromes (MDS) which are still assigned a morphology behaviour code of one and grouped with the 'D codes' in the latest update of the site-based International Statistical Classification of Diseases (ICD-10) [4]. Such radical changes posed significant problems for population-based cancer registries; many struggling to capture all haematological malignancies, particularly patients diagnosed with MDS and chronic myeloproliferative neoplasms [5–7] and continuing to report using the traditional ICD-10 groupings of leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma and myeloma for a number of years [8–11].

In addition to the change in classification and breadth of investigations required to accurately diagnose haematological malignancies (histology, cytology, immunophenotyping, cytogenetics, flow cytometry and clinical data), a major factor impacting on routine cancer registration is the fact that unlike other cancers haematological malignancies are characterized by their ability to progress and transform [1,2]. For example, certain MDS subtypes are, by their nature, disposed to progress to AML and, in order to deal with such phenomena, national and specialized cancer registries have applied a range of different policies [12–15]. In 2010, the USA's SEER (Surveillance, Epidemiology and End Results) program issued guidelines to allow primary AML registrations in patients with a prior MDS registration, unless the two diagnoses were $\leq$21 days apart [15]; the 2001 guidelines, which prohibited such registrations, having resulted in falling AML rates [16–18]. On the other hand, ENCR (European Network of Cancer Registries) and European HAEMCARE guidelines state that only the first tumour, in this example MDS, should be counted in incidence statistics, unless AML progression occurs within three months (90 days), in which case the original MDS code should be replaced by the appropriate AML code [13,14]. As well as variations in case definition, making comparisons between the rates generated by different registries is further complicated by the fact that standard populations with widely differing age structures are often used for age-adjustment. European registries have, for example, generally used the 1976 European standard [19–24], US SEER registries the US 2000 standard [16,17], and registries from elsewhere in the world their own country specific standards and/or the 1996 World standard [25–27].

Since 2001, continued advances in genomics and diagnostic technologies have led to further WHO revisions, and haemato-oncology continues to be one of the most rapidly evolving fields in cancer research [1,2]. Accordingly, to address the need for responsive "real-time" generalizable data on haematological malignancies to inform contemporary clinical practice and research, we established a population-based patient in cohort in the UK in 2004–the Haematological Malignancy Research Network (www.hmrn.org) [28]. Set within a catchment population of over 4 million people, all haematological malignancy diagnoses are made and coded by clinical specialists working at a single integrated haematopathology laboratory; and follow-up data are collected to clinical trial standards. Providing up-to-date information on patients diagnosed 2004–13 and followed through to September 2015, the present report focuses on the occurrence (incidence and prevalence) and outcomes (survival and

Table 1
Total numbers of myeloid diagnoses and de Novo diagnoses: HMRN Sept 2004 to Aug 2013.

	Diagnoses		Males		Females	
Malignancy (International Classification of Disease for Oncology 3rd Edition)	Total	Myeloid de novo (% of total)	Total	Myeloid de novo (% of total)	Total	Myeloid de novo (% of total)
All myeloid malignancies	5231	4945 (94.5)	2868	2691 (93.8)	2363	2254 (95.4)
Acute myeloid leukaemia (AML) (9727, 9861, 9871, 9866, 9895, 9896, 9920)	1411	1190 (84.3)	769	631 (82.1)	642	559 (87.1)
AML, not otherwise specified (9861)	860	825 (95.9)	475	452 (95.2)	385	373 (96.9)
AML with myelodysplasia-related changes (9895)	197	13 (6.6)	121	7 (5.8)	76	6 (7.9)
AML with NPM1 mutation (9861)	104	104 (100.0)	42	42 (100.0)	62	62 (100.0)
Acute promyelocytic leukaemia (APL) (9866)	91	91 (100.0)	47	47 (100.0)	44	44 (100.0)
AML, core binding factor (9871, 9896)	64	64 (100.0)	41	41 (100.0)	23	23 (100.0)
AML, probable therapy related (9920)	61	59 (96.7)	28	27 (96.4)	33	32 (97.0)
AML with MLL (11q23) (9897)	25	25 (100.0)	10	10 (100.0)	15	15 (100.0)
Myelodysplastic syndromes (MDS) (9982–9986)	1194	1188 (99.5)	794	790 (99.5)	400	398 (99.5)
Refractory cytopenia with multilineage dysplasia (RCMD) (9985)	497	495 (99.6)	364	362 (99.5)	133	133 (100.0)
Refractory anaemia with excess blasts (RAEB) (9983)	458	455 (99.3)	291	290 (99.7)	167	165 (98.8)
Refractory anaemia with ring sideroblasts (RARS) (9982)	213	212 (99.5)	135	134 (99.3)	78	78 (100.0)
Myelodysplastic syndrome (5q-) (9986)	26	26 (100.0)	4	4 (100.0)	22	22 (100.0)
Myeloproliferative neoplasms (MPN) (9741, 9875, 9950, 9961, 9962, 9964, 9975. 9875)	2330	2296 (98.5)	1118	1100 (98.4)	1212	1196 (98.7)
Chronic MPNs[a] (9950, 9962, 9975)	1819	1812 (99.6)	820	815 (99.4)	999	997 (99.8)
Chronic myeloid leukaemia (CML) (9875)	318	316 (99.4)	189	188 (99.5)	129	128 (99.2)
Myelofibrosis (9961)	165	140 (84.8)	99	87 (87.9)	66	53 (80.3)
Systemic mastocytosis (9741)	26	26 (100.0)	8	8 (100.0)	18	18 (100.0)
MDS/MPN (9945, 9946, 9975, 9876)	296	271 (91.6)	187	170 (90.9)	109	101 (92.7)
Chronic myelomonocytic leukaemia (CMML) (9945)	239	221 (92.5)	152	140 (92.1)	87	81 (93.1)
MDS/MPN, unclassifiable (9975)	30	24 (80.0)	17	13 (76.5)	13	11 (84.6)
Atypical chronic myeloid leukaemia (9876)	23	22 (95.7)	17	16 (94.1)	6	6 (100.0)

[a] Polycythaemia vera, essential thrombocythaemia, MPNs unclassified.

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