Myeloproliferative neoplasm survival in Europe: A EUROCARE-5 study

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Rationale

Myeloproliferative neoplasms (MPNs) are a group of haematopoietic malignancies resulting from a transformed haematopietic progenitor cell. They are characterised by overproduction of mature functional blood cells. MPNs were historically termed myeloproliferative disorders and have undergone numerous amendments in classification. The 2008 World Health Organisation (WHO) classifies a number of related disorders as MPNs including polycythemia vera (PV), essential thrombocythemia (ET) and primary/idiopathic myelofibrosis (PMF), chronic myelogenous leukaemia, chronic neutrophilic leukaemia, chronic eosinophilic leukaemia and mast cell disease[1]. The classic MPNs are considered PV, ET and PMF. Reported incidence rates for these conditions vary from 0.02 to 2.8 per 100,000 persons[2-4] but are not well characterised with half of patients asymptomatic at diagnosis[5]. Recently the RARECARE working group reported an incidence rate of 1.8 per 100,000 for 'other myeloproliferative neoplasms' in Europe[6].
The incidence of 'other myeloproliferative neoplasms' was **2,24** in the HAEMACARE project. No estimates were provided by PV, ET or PMF[6]. Incidence of PV in the HAEMACARE project was **1.53** [14]
In 2005 an acquired genetic mutation of Janus kinase 2 $(JAK2)_{v617F}$ was found to be present in almost all PV patients and approximately half of ET and PMF patients[7].

PV and ET are indolent neoplasms with better prognosis compared to PMF. Survival of 'other myeloproliferative neoplasms' in Europe was recently reported at 74% with highest 5-year survival rates for ET (90%) followed by PV (84%) and PMF (35%)[6]. A recent Swedish study reported similar 5-year relative survival rates; 97% for ET, 93% for PV and 47% for PMF. Survival rates have improved over time for PV and ET but not PMF and were higher in women than men[8]. Potential explanations for improvements in survival include improved therapeutic strategies and improvements in the treatment of complications such as splanchnic vein thrombosis[9].

The recent investigation of survival in Europe did not investigate survival differences by region, age or gender for PV, ET or PMF[6]. Survival variation by age was reported for PV, PMF, ET in a recent article [15].

Data from EUROCARE-4 has demonstrated wide variation in survival rates of many cancer sites including haematological malignancies[10]. Assessing survival patterns across Europe and identification of variations in cancer survival by country, age,

gender and year of diagnosis may highlight variations in diagnosis, risk factors for complications such as vascular disease, differeces in disease-related and all cause mortality and have implications for targeted therapies which are expanding rapidly and transplantation rates.

Aims
To investigate the survival of patients with classic and other myeloproliferative neoplasms across Europe by year, gender, age and country/region.

Data required
Definition of cases:
Myeloproliferative neoplasms including:
* Chronic myelogenous leukemia (M-9875/3)
* Essential thrombocythaemia (M-9962/3)
* Polycythaemia vera (M-9950/3)
* Chronic Idiopathic Myelofibrosis (M-9961/3)
* Chronic Neutrophilic Leukaemia (M-9963/3)
* Chronic Esinophilic leukaemia (M-9964/3)
* Chronic Myeloproliferative disease, NOS (M-9960/3)

Registries with more than 30% of the MPNs not otherwise specified (Chronic Myeloproliferative disease, NOS (M-9960/3)) will be excluded from the analysis. The following data will be requested for patients meeting the inclusion criteria:
* Sex
* Date of birth
* Date of diagnosis
* Date of death
* Vital Status
* Multiple tumour code
* Underlying cause of death
* Life Tables
* Population data

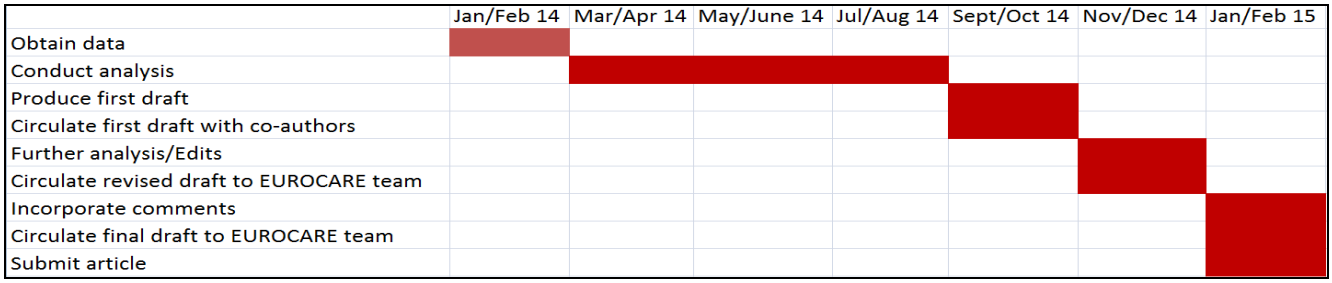
Time Period
Diagnosis 2000-2007, follow up end 2008 (later if available).

Methods of analysis
Registries with data on MPNs will be included in the study and sub-divided into European regions including Northern, Southern, Eastern and Central Europe and UK/Ireland. Registries will be assessed for data quality based on percentage lost to follow up, percentage death certificate only/autopsy cases and percentage not otherwise specified. One and five-year relative survival will be calculated using Ederer-2 for generating expected survival, with age-standardisation using the International Cancer Survival Standard[11]. The relative survival will be estimated as the ration of observed survival compared to the expected survival of individuals in the general population by age and gender. Countries with small numbers will not be reported individually but included in the pooled analyses. Cohort analysis will be applied for all survival analysis except for persons where 5-year follow-up is incomplete, for which the period approach will be utilised[12]. Relative excess risks of death compared to Europe will be derived by taking the ratio of the natural logarithm

of the relative survival rate for each region to that of the European pool of registries. Raw frequencies of each category of disease will be examined by year of incidence and registry (to verify differences year by year) to secular change in classification and completeness of registry data. Survival trend significance will be evaluated as the p-value (two-sided, <0.05) of the slope coefficient deriving from a linear regression on the relative survival trend in Europe grouping by 2000-2003 and 2004-2007.

Separate survival estimates will be undertaken for each of the classic and other myeloproliferative neoplasms individually with particular focus on PV, ET and PMF. Further analysis will be undertaken stratifying survival estimates by gender, age, year of diagnosis and country (in those with sufficient data) and regions where sample size is sufficient. All-cause and disease specific survival will be investigated. The analyses will be undertaken using STATA by Finian Bannon and Mr Glen Titmarsh within the secure network within the Northern Ireland Cancer Registry, Centre for Public Health, Department of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Northern Ireland.

Timeline



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