Clinical and epidemiological studies in myeloproliferative neoplasms

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet öffentligen försvaras i Föreläsningssalen CMM L08:00, Karolinska Universitetssjukhuset Solna

Fredagen den 24 maj, 2013, kl 09:00

av
Malin Hultcrantz
ST-läkare

Huvudhandledare:
Magnus Björkholm
Professor
Karolinska Institutet
Institutionen för medicin, Solna

Bihandledare:
Sigurdur Yngvi Kristinsson
MD, PhD
Karolinska Institutet
Institutionen för medicin, Solna

Paul Dickman
Universitetslektor
Karolinska Institutet
Institutionen för medicinsk epidemiologi och biostatistik

Fakultetsopponent:
Mario Cazzola
Professor
University of Pavia Medical School
Dept of Hematology Oncology
Fondazione IRCCS Policlinico San Matteo

Betygsnämnd:
Maria Feychting
Professor
Karolinska Institutet
Institutet för miljömedicin

Torbjörn Nilsson
Professor
Örebro Universitet,
Institutionen för hälsovetskap och medicin

Hans Wadenvik
Professor
Sahlgrenska Akademin
Göteborgs Universitet
Institutionen för medicin

Stockholm 2013
ABSTRACT

Myeloproliferative neoplasms (MPN), including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), are clonal hematopoietic disorders characterized by excessive terminally differentiated myeloid cells. MPNs can progress to secondary myelofibrosis or acute myeloid leukemia (AML)/myelodysplastic syndromes (MDS). Although progress has been made in the understanding of the pathogenesis and management of MPNs, there are still unresolved issues regarding prognosis, causes of death, and risk factors for leukemic transformation. In patients with hematological malignancies, the risk of suicide and suicide attempts is largely unknown.

We conducted a population-based study to establish patterns of survival in 9,384 MPN patients identified from the Swedish Cancer Registry between 1973 and 2008. Relative survival ratios were computed as measures of patient survival. Relative survival was significantly lower in all MPN subtypes compared to expected survival in the general population, reflected in 10-year relative survival ratios of 0.64 (95% confidence interval (CI); 0.62-0.67) in PV, 0.68 (0.64-0.71) in ET, and 0.21 (0.18-0.25) in PMF, respectively. Excess mortality was observed in patients of all MPN subtypes during all four calendar periods (p <0.001). Nevertheless, survival improved significantly over time (p <0.001); however, the improvement was less pronounced after the year 2000 and was confined to patients with PV and ET. In conclusion, our findings underline the assertion that all MPNs should be considered serious diseases that reduce life expectancy and highlight the need to improve treatment strategies for these patients.

Through the Swedish Cancer Registry and our national MPN cohort we identified 9,563 MPN patients diagnosed between 1973 and 2005 and their 37,643 matched controls to assess excess mortality and causes of death. Cumulative incidence functions, calculated using a flexible parametric model, were used to estimate 10-year probabilities of death with 95% CIs for six categories of causes of death. The 10-year probability of dying from infections in male MPN patients aged 70-79 years at diagnosis were 4.5% (matched controls; 2.3%), from hematological malignancy 13.7% (0.2%), from cardiovascular disease 16.8% (15.0%), from cerebrovascular disease 5.5% (5.1%), from solid tumor 9.7% (11.5%), and from other disorders 24.9% (14.9%). The excess mortality in MPN patients declined due to a decrease in deaths from hematological malignancies during the first calendar period (1973-1982), infections, and in younger MPN patients, from cardiovascular disease. The overall improvement in 10-year mortality, observed in both patients and matched controls over time, was mainly explained by declines in cardiovascular death. In conclusion, the improved survival over time is multifactorial and can only partly be attributed to improved management of the underlying hematological malignancy.

We conducted a nested case-control study to assess the role of MPN treatment and subsequent AML/MDS risk. From a nationwide MPN cohort (n=11,039; diagnosed 1958-2005), we identified 162 patients (cases) with transformation (153 and nine with subsequent AML and MDS diagnosis, respectively) and their 242 matched controls (MPN patients without AML/MDS transformation). Using logistic regression, odds ratios (ORs) were calculated as measures of AML/MDS risk. Forty-one (25%) of the 162 MPN patients with AML/MDS transformation were never exposed to alkylating agents, radioactive phosphorous (P32), or hydroxyurea (HU). The ORs for cases receiving 1 to 499 g, 500 to 999 g, more than 1,000 g of HU were 1.5 (95% CI; 0.6-2.4), 1.4 (0.6-3.4), and 1.3 (0.5-3.3), respectively, for AML/MDS development (not significant). Patients with MPNs who received P32 doses greater than 1,000 MBq and more than 1 g of alkylating agents had a 4.6-fold (2.1-9.8; p<0.002) and 3.4-fold (1.1-10.6; p<0.015) increased risk of AML/MDS, respectively. Thus, the risk of AML/MDS development after MPN diagnosis was not associated with HU treatment at any dosage. The fact that only 32% of patients with AML/MDS transformation received doses found here to be leukemogenic indicates a major role for non-treatment-related factors.

To define incidence and risk factors for suicide and suicide attempts in patients with hematological malignancies, we conducted a population-based study in 47,220 patients with hematological malignancies and their 235,868 matched controls. Using Cox regression, the hazard ratios (HRs) for suicide and suicide attempts (combined end-point) in patients with hematological malignancies was 1.9 (95% CI; 1.5-2.3) compared to matched controls during the first three years after diagnosis. When more than three years had elapsed, there was no excess risk of suicide/suicide attempts (HR 1.1; 0.9-1.4). Patients with multiple myeloma carried the highest risk, HR 3.4 (2.3-5.0), and a pre-existing psychiatric disorder was strongly associated with an increased risk of suicide and suicide attempts (HR 23.3; 16.6-32.6). Although suicides contributed marginally to mortality in patients with hematological malignancies, awareness of risk factors for suicide/suicide attempts can facilitate identification of high-risk patients and enable preventive interventions.