Risk of second primary malignancies in a population-based study of adult patients with essential thrombocytemia

Rajesh Shrestha, Smith Giri, Ranjan Pathak, Vijaya Raj Bhatt

Abstract

AIM: To determine the risk of second primary malignancy (SPM) and survival of patients with essential thrombocytemia (ET).

METHODS: We identified all patients with ET diagnosed during 2001 to 2011 from the Surveillance, Epidemiology and End Results (SEER) 18 database. Actuarial and relative survival methods were used to calculate the survival statistics. We utilized the SEER 13 database to calculate SPM. We used multiple primary standardized incidence ratio (SIR) session of the SEER*Stat software (version 8.1.5) to calculate SIR and excess risk of SPM for ET patients.

RESULTS: Age standardized five-year cause-specific survival was greater for patients < 50 years vs those ≥ 50 years (99.4% vs 93.5%, P < 0.01). Five-year cause
specific survival was lower for men vs women (70.2% vs 79.7%). A total of 201 patients (2.46%) developed SPM at a median age of 75 years. SPMs occurred at an observed/expected (O/E) ratio of 1.26 (95%CI: 1.09-1.45, \( P = 0.002 \)) with an absolute excess risk (AER) of 37.44 per 10000 population. A significantly higher risk was noted for leukemia (O/E 3.78; 95%CI: 2.20-6.05, \( P < 0.001 \); AER 11.28/10000).

CONCLUSION: ET patients have an excellent cause-specific five-year survival but are at an increased risk of SPM, particularly leukemia, which may contribute to excess deaths.

Key words: Essential thrombocythemia; Second primary malignancy; Survival

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Core tip: Second primary malignancy (SPM) contributes to worse survival in essential thrombocythemia (ET). We utilized the Surveillance, Epidemiology and End Results database to analyze the risk of SPM in ET patients diagnosed during 2001-2011. Two hundred and one patients (2.46%) developed SPM at a median age of 75 years. SPMs occurred at an observed/expected (O/E) ratio of 1.26 (95%CI: 1.09-1.45, \( P = 0.002 \)) with an absolute excess risk of 37.44 per 10000 population. A significantly higher risk was noted for leukemia (O/E 3.78; 95%CI: 2.20-6.05, \( P < 0.001 \)). An increased risk of SPM, particularly leukemia, may contribute to excess deaths in ET.

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INTRODUCTION

Essential thrombocythemia (ET) is a subtype of myeloproliferative disorder, which lacks BCR-ABL fusion transcript\(^{[1,2]}\). In United States, the estimated annual incidence is approximately 2.5 cases per 100000 population, whereas the prevalence is estimated to be approximately 24 cases per 100000 population\(^{[3,4]}\). Patients with ET generally have an excellent survival. A large study has shown a median survival of 20 years for the entire cohort of patients with ET and a median survival of 33 years for those < 60 years. Nonetheless, the life expectancy of patients with ET is inferior to sex- and age-matched population\(^{[5]}\). Another study has also demonstrated a median survival of approximately 19 years but the survival was worse than the general population, particularly after the first decade\(^{[5]}\). Risk factors associated with inferior survival include advanced age at diagnosis, leukocytosis and thrombosis; the mutational status of janus kinase 2 (JAK2) and calreticulin (CALR) genes may not definitely influence survival\(^{[7,9]}\). The thrombohemorrhagic events and second primary malignancy (SPM) are among the frequent causes of death in ET\(^{[10-12]}\). ET may progress to other myeloid malignancies such as myelofibrosis, myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)\(^{[2,12]}\). The probability of transformation to leukemia is 1%-5% during the first decade but increases significantly in the subsequent decades\(^{[2,6]}\). Additionally, patients with ET may also develop lymphoid malignancies such as non-Hodgkin's lymphoma (NHL) and solid organ malignancies\(^{[13,14]}\). The treatment with cytotoxic chemotherapy decreases the incidence of thrombohemorrhagic events but may increase the risk of hematological SPM\(^{[2]}\). The risk of SPM may be high in patients exposed to alkylating agents and radioactive phosphorus, more so when used in high doses\(^{[2,12,15,16]}\). A study from Italy has demonstrated that the use of alkylating agents such as melphalan may be associated with a higher risk of developing second hematologic malignancies but not non-hematological malignancies\(^{[17]}\). Prior studies assessing the risk of SPM in ET utilized data mainly from outside the United States. Although the risk of MDS/AML in ET has been studied, the risk of other malignancies is not well determined in United States population-based studies. This United States population-based database analysis aimed to determine the probability of SPM and survival in patients with ET\(^{[18]}\). The influence of age at diagnosis and disease duration on the probability of SPM was also analyzed.

MATERIALS AND METHODS

We utilized Surveillance, Epidemiology and End Results (SEER) database to extract data on all ET patients diagnosed and treated between 1973 and 2011. The SEER is a program of the National Cancer Institute (NCI) that provides cancer data from population-based cancer registries and covers 28% of the total United States population. The database covers data from 25% of all White population, 26% of African Americans, 38% of Hispanics, 50% of Asians, 44% of American Indians and Alaska Natives and 67% of Hawaiian/Pacific Islanders\(^{[19]}\). Patients with ET were identified using International Classification of Diseases for oncology, 3rd edition (ICD)-O-3 code 9962/3 from the SEER 18 registry. Prior studies have used a similar approach in identifying patients with ET from the SEER database\(^{[20,21]}\). Cases with unknown age or survival time and those diagnosed at autopsy and by death certificate only were excluded. SEER started reporting data on chronic myeloproliferative disorders including ET from 2001; as a result our analysis was restricted to cases diagnosed after 2001 only\(^{[21]}\). Actuarial and relative survival methods were used to calculate the survival statistics. We computed...
age-standardized cause-specific survival using the cause-specific death classification available from the SEER registry. Cause-specific survival is a net survival measure that computes survival from cancer related causes of death in the absence of other causes of death. A prior study from SEER registry has shown that cause-specific survival rates may be a reliable alternative to relative survival methods when suitable life tables are not available\(^1\). Relative survival rate, which measures net cancer survival controlling for differences in mortality for causes other than cancer, was defined as the ratio of observed survival of a group of cancer patients to the expected survival of a comparable cohort of cancer free patients. Expected survival was computed using the Ederer I method. All calculations were age standardized to the International Cancer Survival Standard for age 15+ years\(^2\).

For the calculation of SPM, we utilized the SEER 13 registry using patients with ET diagnosed between 2001-2010. Using Warren and Gates criteria as modified by NCI\(^3\), SPM was defined as a metachronous malignancy developing at least six months after the diagnosis of ET. A similar approach for the definition of SPM has been used in prior SEER based studies\(^4,5\). We used multiple primary standardized incidence ratio (SIR) session of the SEER*Stat software (version 8.1.5) to calculate SIR and absolute excess risk (AER) of SPM for ET patients. SIR is obtained by dividing the observed number of second malignancies by the expected number of cases that would occur in a reference population without the index malignancy. Confidence intervals (at 95%) and \(P\)-values were calculated using Poisson exact methods for the ratio of observed to expected events. AER was defined as the excess (observed-expected) number of second cancers in patients with index ET, per 1000 person years at risk. For patients who developed more than one malignancies after the primary disease, all of the subsequent malignancies were counted in the numerator for the calculation of SIR. The strata for SPMs were defined as a priori, and we included at least ten observed occurrences in each stratum.

Statistical analysis was done using SEERstat version 8.1.5 (National Cancer Institute, Bethesda, Maryland) and STATA (StataCorp, College-Station, Texas). Differences between survival rates of two groups were analyzed using the Z test for comparison of population proportions. All \(P\)-values were two sided and the level of significance was chose at 0.05. Institutional review board waiver was obtained from the University of Nebraska Medical Center Institutional Review Board prior to conducting this study.

### RESULTS

A total of 8152 cases were identified from the SEER 18 registry, out of which 36 cases met the exclusion criteria (23 had unknown survival and 13 cases diagnosed prior to 2001). The remaining 8116 cases included 39.4% males (\(n = 3195\)) and 60.6% (\(n = 4921\)) females, and had a median age at diagnosis of 68 years (range < 1-107) (Table 1). Only 17 patients were less than 18 years old (0.7% of total). Ethnicity included 78% Whites, 12% African Americans, 7% others (American Indian/Alaska Native or Asian/Pacific Islander) and 3% unknown. The median year at diagnosis was 2007 (range 2001-2011).

The overall 1-year and 5-year age-standardized cause-specific survival of the study cohort was 99.1% and 94.9% respectively. The 5-year cause-specific survival was significantly different for patients below 50 years vs those 50 years and above (99.4% vs 93.5%; \(P < 0.01\); Figure 1A) as well as for men vs women (93.1% vs 96.0%; \(P < 0.01\); Figure 1B) (Table 2). Similarly, the age-standardized 1-year and 5-year relative survival rates were 96.6% and 88.4% respectively.

At a median follow-up of 3 years (range, 6-129 mo), 201 patients (2.46%) out of 2913 patients with ET developed SPM. The median age at diagnosis was 75 years (range, 39-94 years). None of the patients less than 18 years old developed SPM. SPMs occurred at an SIR of 1.26 (95%CI: 1.09-1.45; \(P = 0.002\)) with an AER of 37.44 per 10000 population. The risk for developing leukemia (SIR 3.78; 95%CI: 2.20-6.05, \(P < 0.01\); Figure 1A) as well as for men vs women (93.1% vs 96.0%; \(P < 0.01\); Figure 1B) (Table 2). Similarly, the age-standardized 1-year and 5-year relative survival rates were 96.6% and 88.4% respectively.

### Table 1 Characteristics of patients with essential thrombocythemia

| Characteristics | n (%) |
|-----------------|-------|
| Age             |       |
| < 50 yr         | 1600 (19.7) |
| 50-70 yr        | 2958 (36.5) |
| > 70 yr         | 3558 (43.8) |
| Sex             |       |
| Male            | 3195 (39.4) |
| Female          | 4921 (60.6) |
| Race            |       |
| White           | 6332 (78) |
| African American| 971 (12) |
| Other           | 576 (7.1) |
| Unknown         | 237 (2.9) |
| Marital status  |       |
| Single/unmarried| 1152 (14.2) |
| Married         | 3815 (47) |
| Divorced/separated/widowed | 2125 (26.2) |
| Unknown         | 1024 (12.6) |
| Year at diagnosis|       |
| 2001-2005       | 3035 (37.3) |
| 2006-2010       | 4251 (52.4) |
| 2011-present    | 840 (10.3) |

\(^1\)Other race indicates Asian, Hispanic, Native North American and other racial groups.
of 24 mo, the risk of SPM in general (O/E 1.31, 95%CI: 1.1-1.55, P = 0.002), kidney cancer (O/E 3.27, 95%CI: 1.5-6.21, P = 0.003), and leukemia (O/E 3.72, 95%CI: 1.86-6.66, P < 0.001), particularly AML (O/E 7.08, 95%CI: 2.6-15.4, P < 0.001) was determined to be higher.

The risk of AML was noted to be higher among all age groups (Table 5). The risk of SPM in general (O/E 1.78), solid tumors (O/E 1.75), and AML (O/E 12.7) were noted to be higher among patients 18-60 years old. Among patients ≥ 60 years old, the risk of kidney cancer (O/E 2.42) and leukemia (O/E 3.78), particularly AML (O/E 7.06) was higher.

DISCUSSION

Our study demonstrates excellent age-standardized cause-specific five-year survival with 99.4% of patients below 50 years of age and 93.5% of patients above 50 years of age alive at 5 years. The five-year overall survival was significantly lower in patients over 50 years of age as well as in males as compared to females.

A Mayo clinic study demonstrated significantly higher OS in patients younger than 60 years vs those 60 years or older (32 years vs 19 years, P < 0.001). While OS was similar to general population in the first decade of disease [risk ratio (RR), 0.72; 95%CI: 0.50-0.99], OS was significantly worse after the first decade (RR, 2.21; 95%CI: 1.74-2.76, at 20 years and RR, 3.37; 95%CI: 1.84-5.65, at 30 years). This is consistent with fact that the incidence of SPM such as leukemia and myelofibrosis is higher after the first decade. A number of factors may determine the OS of these patients. The prognostic factors associated with the poor outcomes are age at diagnosis of ≥ 60 years, leukocyte count more than 15 × 10^9/L, a history of thrombosis, diabetes, hypertension and tobacco smoking.

In our study, a significantly elevated risk was noted for the development of AML and kidney cancer and especially after 24 mo of diagnosis of ET. Such increased risk has been noted in other studies also. In a retrospective population-based Danish cohort study, patients with ET, compared to those without, had a higher risk for developing hematological and solid malignancies with the SIR of 5 (95%CI: 3.6-6.9) and 1.2 (95%CI: 1.1-1.6).
In our study, the risk of SPM varied based on the age at diagnosis of ET and the follow-up duration. The risk of developing leukemia, particularly AML, can affect patients of all age groups and persists over time. Clinical trials on early detection of SPM may be considered in patients with ET. Additionally, patients with ET should be encouraged to undergo age and sex-
appropriate cancer screening tests.

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COMMENTS

Background

Patients with essential thrombocythemia (ET) have an excellent cause-specific five-year survival but are at an increased risk of second primary malignancy (SPM), particularly leukemia, which may contribute to excess deaths.

Research frontiers

A few United States studies have evaluated the risk of myelodysplastic syndrome/acute myeloid leukemia (AML) in ET but not the risk of other hematological or solid-organ malignancies.

Innovations and breakthroughs

This large Surveillance, Epidemiology and End Results database-based study confirmed an increased risk of SPM in patients with ET. A significantly higher risk was noted for leukemia. An increased risk of SPM, particularly leukemia, may contribute to excess deaths in ET. The risk of developing leukemia especially AML was increased after 6 mo of diagnosis of ET and persisted beyond 24 mo of follow-up, consistent with prior studies. Prior studies have shown conflicting results on the impact of age on the risk of SPM. In this study, the risk of overall SPM was higher in patients younger than the age of 60 years, however, the increased risk of kidney cancer and leukemia was noted in those above 60 years. The risk of leukemia, particularly AML, can affect patients of all age groups and persists over time.

Applications

The knowledge of an increased risk of SPM in patients with ET has implications in patient education, planning of preventive cancer screening strategies and may serve as a foundation for future research targeted at understanding the tumorigenesis in these patients.

Terminology

SPM: A metachronous malignancy developing at least six months after the diagnosis of ET. Relative survival rate: Ratio of observed survival of a group of cancer patients to the expected survival of a comparable cohort of cancer free patients. It measures net cancer survival controlling for differences in mortality for causes other than cancer; Cause-specific survival: A net survival measure that computes survival from cancer-related causes of death in the absence of other causes of death; Standardized incidence ratio: Ratio obtained by dividing the observed number of second malignancies by the expected number of cases in a reference population without the index malignancy; Absolute excess risk: Excess (observed-expected) number of second cancers in patients with ET, per 1000 person years at risk.

Peer-review

The paper is about an interesting topic. It is well written and the methods are sound. The conclusions are consistent with the results.

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