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Clinical prognostic factors and outcomes of essential thrombocythemia when transformed to myelodysplastic syndromes and acute myeloid leukemia☆

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ABSTRACT

Transformation of essential thrombocythemia (ET) to myelodysplastic syndromes or acute myeloid leukemia is infrequent, comprising 1–5% of cases with dismal clinical outcome. Studies on prognosis in ET patients with leukemic transformation are limited. The large cohort included 40 patients (1990–2014) with ET transformation (median age of 59 years, M:F of 1:1). Median time from ET diagnosis to transformation was 76 months (26–481) with median follow-up time of 15 years. Advanced age, myelofibrosis (grade 2–3), and leukocytosis at the time of transformation were associated with inferior OS from transformation ($p < 0.05$). Given rarity of the clinical scenario, multicenter efforts are encouraged.

1. Introduction

Essential thrombocythemia (ET) is a nonreactive clonal myeloproliferative neoplasm (MPN) in which sustained megakaryocyte proliferation leads to an increase in the number of circulating platelets [1]. It represents the second-most common MPN in the United States, with an annual incidence rate of approximately 0.6–2.5 cases per 100,000 persons per year [2]. With advanced molecular diagnosis, the incidence rate of ET has increased by 31% according to the most updated data from the Surveillance, Epidemiology, and End Results [3]. The median age at diagnosis is approximately 50–60 years without male or female predominance and the median OS is approximately 20 years [4].

The pathologic cause of ET is unclear, and the role of histopathology in diagnosis of ET is controversial [5]. ET is neither a cytogenetically nor a morphologically defined disease entity, and, alone among the other MPNs like polycythemia vera, primary myelofibrosis, and chronic myelogenous leukemia, ET is the only disease that is currently diagnosed by exclusion of both reactive thrombocytosis and other chronic myeloid disorders. The 2008 World Health Organization (WHO) classification requires the following criteria to establish the diagnosis of ET [1]: sustained platelet count of $\geq 450 \times 10^9$/L; bone marrow biopsy finding of megakaryocytic proliferation with large and mature morphology; not meeting WHO criteria for other BCR-ABL1-positive or BCR-ABL1-negative MPNs, myelodysplastic syndrome (MDS), mixed myelodysplastic and myeloproliferative neoplasms (MDS/MPN), or other myeloid neoplasms; and demonstration of Janus kinase 2 *(JAK2) V617F* mutation or other clonal markers such as myeloproliferative leukemia virus oncogene (*MPL*) or calreticulin (*CALR*)

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Table 1
Patient characteristics.

Characteristic	*N* (% or range)
Total number of patients	40 (100%)
Age at ET diagnosis, years	
Median	59
Range	19–72
Age at ET transformation, years	
Median	68
Range	47–78
Time from ET diagnosis to transformation, years	
Median	6.3
Range	2.2–40.1
Time from ET diagnosis to MDS transformation, years	
Median	5.75
Range	2.2–26.7
Time from ET diagnosis to AML transformation, years	
Median	8.08
Range	2.2–40
Gender	
Male	19
Female	21
ET treatment	
Hydroxyurea alone	21
Anagrelide alone	5
Hydroxyurea and anagrelide	12
Busulfan	1
Uracil mustard	2
Interferon	1
Transformation	
MDS	16
MDS/AML	11
AML	13
Blasts < 20% at transformation	25 (62.5%)
Blasts > 20% at transformation	15 (37.5%)
AML subtype	
AML with myelodysplasia-related changes	11
AML without mutation	3
AML with mutation	2
Acute myelomonocytic leukemia	1
Acute erythroid leukemia (erythroid/myeloid)	NA
Acute megakaryoblastic leukemia	1
AML, no further subclassification	6
MDS or MDS/MPN	
Low grade (RCUD, RCMD, MDS-U)[a]	3
High grade (RAEB-I and RAEB-II)	8
MDS/MPN (CMML, MDS/MPN, NOS)	16
MDS according to IPSS	
Low	6
Intermediate—1	9
Intermediate—2	8
High	4
Fibrosis grade at ET transformation	
0–1	5 (12.5%)
2–3	30 (75%)
Unknown	5 (12.5%)
JAK-2 status	
Positive	14
Negative	12
Unknown	14
Cytogenetics status	
Normal	8
Abnormal (non-complex)[b]	13
Complex[b]	14
Missing	5
Vital status	
Alive	14 (35%)
Dead	26 (65%)
Peripheral blood counts at transformation	
Hemoglobin (g/dL)	9.8 (7.4–12.9
White blood cells (k/uL)	7.42 (1.5–105.6)
Platelets (k/uL)	137 (9–714)
MDS/AML treatment	
Thalidomide	1
Azacitidine	22
Decitabine	7
Lenalidomide	9
Androgen	1
7 + 3	5
CLAG	10
MEC	1
Bone marrow transplant	7
Clinical trial	5

RCUD: refractory cytopenia with unilineage dysplasia, RCMD: refractory cytopenia with multilineage dysplasia, MDS-U: myelodysplasitc syndrome, unclassifiable, RAEB-I and RAEB-II: refractory anemia with excess blasts type I or type II, MDS/MPN: myelodysplastic and myeloproliferative neoplasm, CMML: chronic myelomonocytic leukemia, IPSS: international prognostic scoring system.

[a] One each for RCUD, RCMD and MDS-U, respectively.

[b] Complex cytogenetic abnormalities are defined as having ≥3 chromosomal abnormalities identified.

mutation [6,7]. The three major mutations involving *JAK2 V617F*, *CALR*, and *MPL* genes are reported in 55%, 25%, and 4% of ET patients, respectively [8]. Recent studies have shown that 60–80% of ET patients without *JAK2 V617F* or *MPL* mutation harbor *CALR* mutation, which assists in establishing the diagnosis of ET in double JAK2V617F/MPL-negative patients [8–10].

Acute myeloid leukemia (AML) with or without antecedent MDS transformation is one of the late complications and considered to be the most rare incidence among all MPNs [11]. The reported risk of transformation to MDS or AML in patients with ET has varied in the literature but outcomes remain poor [12]. The incidence rate of MDS transformation ranges from 0% to 3% [13,14], whereas the incidence rate of leukemic transformation ranges from 0.6% to 5% [8,15], with elapsed time to MDS and/or AML conversion in most studies being between 1.7 to 16 years [15]. Given the paucity of transformation to MDS and AML in patients with ET, it remains unclear whether only extrinsic treatment-related factors versus intrinsic ET-related factors, or the combination, play a role in the transformation of ET to MDS or AML. ET treatment and its potential risk of leukemic transformation remain an area of controversy and a serious challenge, particularly for ET patients who are diagnosed early in life with a potential need of different cytoreductive therapies that could play a role in their potential transformation in the future. Our study aims to better understand prognostic factors in patients with ET who transformed to MDS or AML.

2. Methods

After obtaining Institutional Review Board approval, we conducted a review of our patient registry at Moffitt Cancer Center between 1990 and 2014 to identify patients who had a pathologically confirmed ET and transformed to MDS and/or AML. All bone marrow biopsies performed at Moffitt Cancer Center or available bone marrow slides submitted from outside facilities were reviewed by two hematopathologists to confirm the initial diagnosis of ET as well as the transformation to MDS or AML. All patients included in this cohort met the 2008 WHO criteria to establish the initial diagnosis of ET, and transformation from ET to MDS and/or AML, as well as their subtypes according to 2008 WHO classification (Table 1).

All bone marrow biopsies with Gomori silver impregnation for reticulin were graded for reticulin fibrosis using a modified scoring