

Should Chemotherapy be Administered for Essential Thrombocythemia (ET) Patients with Leukemic Transformation?

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ABSTRACT

Introduction: Essential Thrombocythemia (ET) is a clonal myeloproliferative disease presenting predominantly with thrombocytosis. One of its rare complications is leukemic transformation (LT). Once leukemic transformation occurs, prognosis is dismal. We aim to determine the disease profile of LT in our ET patients and evaluate if chemotherapy can alter prognosis.

Methods: Clinical data of all patients diagnosed and treated with ET from 1999 to 2008 in the Department of Hematology, Singapore General Hospital, were captured in the Myeloproliferative Disease(MPD) Registry. ET patients with LT were selected. Patient characteristics, disease profile, including ET treatment, duration from ET diagnosis to LT, prior myelofibrosis (MF) history, type of chemotherapy, response and eventual survival were recorded.

Results: Two hundred and thirty ET patients were diagnosed and treated from 1999 to 2008. Six patients had LT (2.6%). All were Chinese. Four were females. Age range was 47-70 years (mean 61.2 years). Transformation to acute myeloid leukemia (AML) was seen in 5 patients, after a latency period of 3-28 years. Acute biphenotypic leukemia was diagnosed in 1 patient 4 years after ET diagnosis. All patients had received hydroxyurea. There was no prior evolution to MF. Complex cytogenetics were seen in all cases. Three patients treated conservatively died within 1 month. The other 3 patients did not go into durable complete remission despite chemotherapy and succumbed within 9 months.

Conclusions: Leukemic transformation in ET, though rare, is associated with grave prognosis. Outcome with chemotherapy is dismal. More studies are needed to evaluate if alternative treatment can improve survival.

Keywords: BCR-ABL negative, blasts, induction

INTRODUCTION

Essential Thrombocythemia (ET) is a clonal myeloproliferative disease involving a hematopoietic stem cell with the predominant manifestation of thrombocytosis¹⁻². It is associated with thrombohemorrhagic complications. ET may also transform into other Philadelphia-negative myeloproliferative diseases (MPD), including polycythemia vera (PRV), myelofibrosis (MF) and acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)²⁻³. Variable rates (1.3% - 13.1%) of AML or MDS transformation have been

reported in the literature⁴⁻⁸. It is known that blastic transformation may be related to the use of alkylators, radiation or other DNA damaging agents during treatment⁹. AML transformation is associated with a dismal prognosis. Median survival is only six weeks for patients receiving supportive treatment. Responses to chemotherapy are not durable. It is reported that long-term survivors had all received stem cell transplant either as first therapy or in first remission¹⁰.

Our aims in this study are to determine the disease profile of patients with ET who transformed to acute leukemia and to determine if chemotherapy can alter prognosis.

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Table 1. Clinical data of 6 ET patients with leukemic transformation.

Patients	Age at ET diagnosis (years/gender)	Age at acute leukemia diagnosis (years)	Disease transformation	Latency (years)	ET treatment	Prior MF	Acute leukemia karyotype	Time from leukemia to death (months)	Chemotherapy treatment
A	25/F	53	AML	28	HU,BU, chlorambucil, ³² p	no	complex	9	IA, FLAG, dexamethasone, vinblastine, HIDAC
B	39/F	47	AML	8	HU	no	complex	<1	No
C	60/F	65	ABL	4.3	HU, anagrelide, IFN	no	complex	20	IA, VCR, HIDAC, FLAG
D	57/F	67	AML	10	HU	no	complex	1	No
E	56/M	70	AML	14	HU, anagrelide, IFN	no	complex	7	Decitabine, HU
F	65/F	68	AML	3	HU	no	complex	<1	No

ABL: acute biphenotypic leukemia, AML: acute myeloid leukemia, BU: busulphan, dexamethasone, FLAG: fludarabine, Ara-C, G-CSF (granulocyte colony stimulating factor), HIDAC: high-dose Ara-C, HU: hydroxyurea, IA: Idarubicin, Ara-C, IFN: interferon, MF: myelofibrosis, 32P: radioactive phosphorus, VCR: vincristine

METHODS

The Department of Hematology, Singapore General Hospital, maintains a Myeloproliferative Diseases (MPD) Registry where all clinical data of patients diagnosed with ET from 1999 to 2008 were captured. This is a computerized database, approved by the SingHealth Institutional Review Board. The diagnosis of ET was made based on either the Polycythemia Vera Study Group (PVSG) criteria⁴ or WHO criteria¹¹ depending on the date of diagnosis. A review of the database was made to select patients with ET who had transformed to acute leukemia. Leukemic transformation was defined as persistent elevation in peripheral blood or bone marrow blasts of more than 20%. Upon identifying these patients, their characteristics, disease profile including diagnosis of ET, treatment, length of time from ET diagnosis to leukemia, history of prior myelofibrosis, response to chemotherapy, eventual outcome and survival were recorded. As the incidence of leukemic transformation is low at less than 5%, the patient numbers were expected to be small. The data collected on these patients were then analysed.

RESULTS

Two hundred and thirty ET patients were diagnosed and treated between 1999 and 2008. Six patients had leukemic transformation resulting in an

incidence of 2.6% (6/230). Clinical data of these patients are summarized in Table 1.

Of these 6 patients, 4 were females. All were Chinese. ET was diagnosed between the ages of 25–65 years old (mean 50.3 years). The age at diagnosis of acute leukemia ranged from 47–70 years (mean 61.2 years). Transformation to acute myeloid leukemia (AML) was seen in 5 cases while 1 patient's disease transformed to acute biphenotypic leukemia (ABL), in which leukemic blasts express both myeloid and lymphoid antigens. The latency period (time interval between ET diagnosis and acute leukemia transformation) ranged from as short as 3 years to as long as 28 years.

Prior ET Treatment

All 6 patients received hydroxyurea (HU), either alone or in combination at some point in their course of treatment for ET. Patient (A) was diagnosed to have ET at age 25 years and was on HU for 28 years. She also received busulphan, chlorambucil and radioactive phosphorus (³²P) during the course of ET treatment. Patients (B), (D) and (F) were treated solely with HU, for 8, 10 and 3 years respectively. Patient (C) was diagnosed with ET at age 60 years and was on HU, anagrelide and interferon (IFN) in various combinations for 4 years before disease

Table 2. Clinical profile of 3 patients given chemotherapy.

Patients	Age at leukemia diagnosis (years)	Chemotherapy given	Cause of death	Overall survival (months)
A	53	IA,FLAG,dexa, vinblastine, HIDAC	Pneumonia, refractory disease	9
C	65	IA, VCR, HIDAC, FLAG	Sepsis, refractory disease	20
E	70	Decitabine, HU	Pneumonia, refractory disease	9

Dexa: dexamethasone, FLAG: fludarabine, Ara-C, GCSF(granulocyte colony stimulating factor), HIDAC: high-dose Ara-C, HU: hydroxyurea, IA: Idarubicin, Ara-C, VCR: vincristine

transformation to ABL. Patient (E) was also treated with HU, anagrelide and IFN in various combinations for 14 years before disease transformation to AML.

Evolution to Myelofibrosis

There was no evolution to myelofibrosis prior to leukemic transformation in these 6 patients.

Cytogenetics of Acute Leukemia

Cytogenetics of all 6 leukemia cases were complex, involving multiple structural and numerical abnormalities.

Patient (A): 46,XX, del(4)(?q31q35), inv(5)(q15q34), del(7)(q11.1), -9,-21,+2mar[19]/ 46,XX[1]

Patient (B): 41-45, XY, der(2) t(2;17)(p11.2;q12), add(4)(q32), del(5)(p15q31), -7, -12, -13, -17, +1[2mar[cp9]/ 46 XY[11]

Patient (C): 46, XX, t(8;21)(q22;q22), der(9) t(1;9)(q12;q34), add(14)(p13), del(20)(q11.2) [cp20]

Patient (D): 45, XX, -1, add(5)(q31), add(9)(q12), add(11)(q14), der(16) t(1;16)(q11;q22), der(17) t(1;17)(p13;p11.2), del(18)(q21q23), der(20)t(9;20)(q21;q11.2)[cp12]/ 96, XXX, -X, -1, -4, +6, add(7)(q11.2)X2, +8, add(9)(q12)X2, +10, del(16)t(1;16)X2,der(17) t(1;17), +18, del(18)(q21q23)X2, +19, +21, +mar[cp6]/ 46, XX[1]

Patient (E): 42~52, XY, add(3)(p13), add(4)(q31.1), -5, -7, add(16)(p11.2), -17, -17, -21, add(22)(q11.2), add(22)(q11.2), +2~4mar[cp20]

Patient (F): 38~45, XX, -4, add(4)(p11), der(4)t(4;14)(p12;q11.2)ins(4;?)(p12;?), -5, add(5)(p13), add(5)(p11),der(5)t(5;14)(p13;q11.2)ins(5;?)(p13;?)-7, -7, add(7)(q11.2), -9, der(9;15)(q10;q10), -11, -13, add(130(p11.2), -14, der(14;15)(q10;q10), add(15)(p11.1), -16, add(17)(p11.2), -18, add(18)(p11.2), der(18)t(18;21)(p11.1;q11.2), -21, add(21)(q22), -22, del(22)(q13)[cp20]

JAK2 mutation

JAK2 mutation studies were not performed in these patients as the test was not available at the time of these patients' diagnoses of ET.

Treatment and outcome of leukemic transformation

Three patients (B, D, F) were treated conservatively and died within one month of leukemia diagnosis. Chemotherapy could not be initiated for Patient (B), who was diagnosed with AML at 47 years of age, as he had a severe pneumonia and renal failure. He eventually succumbed to these. Patient (D), a 67 year old woman with a 10-year history of ET, could not be given chemotherapy upon leukemia diagnosis as she very quickly succumbed to sepsis. Patient (F) was 68 years old on diagnosis of AML and died of sepsis as well.

The other 3 patients (A, C, E) who received chemotherapy had longer overall survival (OS) but eventually succumbed to refractory leukemia (Table 2). Overall survival was defined as the length of time from acute leukemia diagnosis to death. Patient (A) received standard idarubicin and cytarabine (IA 3+7) induction chemotherapy for AML M2 but did

not achieve complete remission (CR). Bone marrow studies showed residual blasts. She was reinduced with fludarabine-based chemotherapy (FLAG) which was not successful in bringing the disease into remission. She developed pneumocystis jiroveci pneumonia and took 2 months to recover. Salvage high-dose cytarabine (HIDAC) chemotherapy was then initiated. Neutropenic sepsis, pneumonitis and drug-induced transaminitis complicated this course of chemotherapy. Both the patient and her family declined further treatment. Her subsequent clinical course was complicated by bleeding and sepsis. She finally succumbed to refractory leukemia 9 months after diagnosis.

Patient (E) was diagnosed to have AML at 70 years of age, after being treated with a varying combination of HU, anagrelide and IFN for 14 years. In view of his age and other medical conditions of Parkinson's Disease and benign prostatic hyperplasia, he was started on decitabine, a hypomethylating agent. His hospitalization stay was complicated by neutropenic sepsis requiring multiple antibiotic treatment, congestive cardiac failure, *Clostridium difficile* diarrhoea, methicillin-resistant *Staphylococcus aureus* and *Enterococcus* infections. A decision for palliative care was made and the remaining few months of the patient's life was complicated by frequent blood transfusions and pneumonia, to which he finally succumbed, 9 months from the diagnosis of leukemic transformation.

The last patient, Patient (C), who received chemotherapy, had a background history of hypertension and atrial fibrillation. Diagnosed with ET at age 60 years, she received various combinations of HU, anagrelide and IFN. Acute biphenotypic leukemia (ABL) was diagnosed approximately 4.3 years later. She responded initially to induction chemotherapy with idarubicin, cytarabine and vincristine. This was followed by consolidation chemotherapy. However, she relapsed 10 months later and did not achieve CR with multiple salvage regimens including HIDAC and FLAG. She developed multiple episodes of sepsis, including fungal infection and finally succumbed 20 months after diagnosis of ABL.

In summary, all 3 patients who were treated with chemotherapy did not achieve a durable CR and died of infectious complications secondary to refractory disease.

DISCUSSION

(i) Incidence of leukemic transformation (LT) and risk factors

Progression of ET to AML, preceded or not by myelodysplastic syndrome (MDS), is rare and has been reported in various studies to have an incidence of 1.3-13.1%⁴⁻⁸. Our incidence of LT was 2.6%, from our fairly large cohort of 230 ET patients. Reported incidence rates are confounded by the inherent risk of leukemic transformation in ET and the use of agents, such as hydroxyurea (HU), alkylating agents and radioactive phosphorous, in the treatment of ET. Other risk factors for LT include prior evolution to myelofibrosis (MF) and longer disease duration. Patients with MF have higher rates (up to 20%) of leukemic transformation. Sequential evolution to AML after prior transformation to MF is less well described than conversion of ET to AML or conversion of ET to MF^{5,7,12}. In our series of 230 patients, none of the patients with leukemic transformation had prior MF transformation. In contrast, Chin et al¹³ who reported on a multi-center study conducted among 231 consecutive Chinese patients with ET in 2005, found that prior MF is a major risk factor for evolution to AML. In their series, 7 patients developed MF after a median latency of 8 years, 2 of whom later developed AML. The cumulative probability of MF transformation was 9.7% at 10 years. This difference in the studies could be due to small numbers of patients who developed MF or that the MF phase of the disease was not recognised in these small numbers of patients. Other risk factors for LT reported include increased age, high leucocyte count, anemia and platelet count $\geq 1,000,000/\mu\text{L}$ ^{13,14} at diagnosis.

The controversy regarding the leukemogenicity of HU remains an issue of much debate. Hydroxyurea, a non-alkylating myelosuppressive agent that inhibits DNA synthesis, also inhibits DNA repair. Several nonrandomized studies have either supported or refuted a significant increase in leukemic conversion associated with long-term use of HU^{8,15-17}. Transformation to leukemia among patients with ET receiving HU as the sole treatment varied in frequencies between 0-5%. In a study by Sterkers et al⁸ who reported on a series of 357 patients followed for a median of 8 years, the incidence of conversion to myelodysplastic syndrome (MDS) or AML was 4.5%. This risk was 3.5% in patients treated with HU alone and 14%

in patients receiving HU in combination with 32 P, busulfan or pipobroman. Similar results were obtained by other investigators^{4,6,8}.

In contrast, in a large retrospective study of 435 patients with ET, the 15-year cumulative risk of AML (2%) was not significantly influenced by single agent chemotherapy of any kind, including use of HU¹⁸. Similarly, Cortelazzo¹⁹ and Harrison²⁰, in 2 randomised trials, showed that the risk of LT was not adversely affected by the use of HU alone. Hence, presently, there is no hard evidence to implicate HU use in ET as leukemogenic. Nevertheless, it is legitimate to be concerned about the potential risk of mutagenicity with HU and avoid its use where the benefit of HU is unproven.

In our series of 6 patients, 3 (B, D, F) received HU solely for treatment of ET for durations of 8, 10 and 3 years before LT. Patient B was diagnosed with ET at age 39 years, a relatively young age. He was on HU for 8 years before LT. However, the other 2 patients (D,F) were relatively older at ET diagnosis (57 and 67 years) and received HU for 10 and 3 years respectively. It is difficult to determine the contributory roles of prolonged use of HU and the intrinsic propensity of ET evolution to LT, to leukemogenicity in these patients. One can only speculate that both could have contributed to eventual leukemic event. The other 3 patients received a combination of therapies, all of which included HU at some point in their disease course. Patient (A) was diagnosed with ET at a young age of 25 years and had received busulphan, chlorambucil and 32P, in addition to HU, for 28 years. All these agents have been implicated in leukemogenesis²². Given the long duration of use of these multiple agents and the duration of the primary disease itself, it was not unexpected that this patient had leukemic transformation. The other 2 patients received a combination of HU, anagrelide and interferon (IFN) for 4 and 14 years before LT. To date, anagrelide is not mutagenic²³ and there is no evidence suggesting that it is leukemogenic²². Interferon is also not known to be leukemogenic²². One can only speculate that leukemogenicity in these patients could be due to the natural progression of ET disease, with or without the leukemogenic contribution of HU.

In essence, the question of whether LT in ET is a natural progression of disease, a secondary sequel

of treatment or a combination of both remains difficult to evaluate.

(ii) Cytogenetics abnormalities in LT

Sterkers et al⁸ found that, in a large series of 357 patients, with prolonged follow-up evaluation, MDS and AML occurring after HU treatment often had a 17p deletion (41%). Prolonged use of HU in ET may lead to or at least increase the risk of MDS and AML with loss of 17p chromosomal material (17p-). 17p- chromosomal abnormality is due to unbalanced translocation, monosomy 17 or to i(17q) and is associated with presence of pseudo Pelger-Huet hypolobulation and small vacuoles in neutrophils and with p53 mutation²⁴. The possible association between HU therapy and 17p- anomaly remains unanswered. This anomaly was often associated with other complex abnormalities and was not found to be specific to either HU treatment or ET²⁵. Bernasconi et al²⁴ concluded in their paper that 17p-, trisomy 1q and monosomy 7q were not related to natural history of ET and its genetic instability but they might be induced by the type of cytoreduction therapy given. 17p deletions were discovered only in HU-treated patients and they developed solely at the time of disease evolution. Deletion or loss of 5q, 17p and complex karyotype were all closely related to p53 mutation and to previous chemotherapy with alkylating agents.

All 6 of our ET patients with LT showed complex chromosomal abnormalities, including multiple structural and numerical abnormalities. Chromosome 17 abnormalities (including translocation, deletion) were seen in 4 of these 6 patients. In addition, they had abnormalities involving chromosomes 5 and 7. One of the remaining 2 patients had abnormalities involving chromosomes 5 and 7, while the other had chromosome 1 abnormality. One may speculate that these abnormalities were the result of cytoreductive therapies they had received. Unfortunately, cytogenetics at the diagnosis of ET were not available for these patients. Indeed, Gangat et al²⁶ reported that cytogenetic abnormalities at ET diagnosis are relatively uncommon and do not predict evolution into more aggressive myeloid disorders, or inferior survival.

(iii) Prognosis and Treatment of LT in ET patients

It is well reported that survival following leukemic transformation of myeloproliferative

disease is dismal regardless of the underlying myeloproliferative histology. Median survival is usually 3 months or less²¹. Tam et al¹⁰ reported that the length of antecedent bone marrow disease, number and type of prior therapies and the presence of complex cytogenetics (with the exception of chromosome 17 abnormalities) all had no impact on survival. The only cytogenetic category to have an effect on survival in this study was the presence of chromosome 17 abnormalities. These have been previously reported in LT in ET⁸ and associated with treatment resistance and poor survival in other hematologic malignancies including chronic lymphocytic leukemia²⁷, non-Hodgkin's lymphoma²⁸ and multiple myeloma²⁹.

In patients treated with induction chemotherapy for leukemic transformation of myeloproliferative disease, the major reason for treatment failure was the non-durable complete remission (CR) following chemotherapy, with all patients invariably relapsing at a median of only 5 months. It was postulated that this may be due to chemoresistance in the leukemic clone and/or failure to eliminate the myeloproliferative disease ancestral cell, which may then lead to relapse¹⁰. The underlying myeloproliferative disease clone was not eradicated by induction chemotherapy. In this study¹⁰, it was striking that the only long-term survivors were patients who had received allogeneic transplantation either as first therapy or in first remission.

All of our 6 patients with leukemic transformation had complex cytogenetics, including abnormalities in chromosome 17 in 4 of them. Patients A, C and E received chemotherapy but did not achieve durable CR and succumbed to refractory leukemia eventually. These patients did not survive long enough for stem cell transplant as it was the institution's practice to offer transplant for patients whose disease was in CR. In our series, patients on supportive treatment (B, D, F) succumbed within 1 month of leukemia diagnosis while patients who received chemotherapy succumbed within 9 months, from complications of refractory disease. This demonstrated the aggressiveness of the secondary leukemia and confirmed the dismal prognosis of leukemic transformation reported in other studies²¹. These results suggested that induction chemotherapy may not be the ideal option for ET patients who transformed to leukemia. Based on our results, for subsequent

patients, we might consider the role of stem cell transplant as first treatment option or for patients in first remission, as it was suggested that long-term survivors reported in literature had received this.

CONCLUSIONS

Leukemic transformation in ET patients is rare, with an incidence of 2.6% in our series of 230 ET patients, a rate comparable to reported incidences. Complex cytogenetics at LT were seen in all of our patients with abnormalities involving chromosomes 17, 5, 7 occurring predominantly. Chromosome 17 abnormalities are associated with treatment resistance and poor survival. Leukemic transformation may be related to the use of alkylators, radiation or other DNA damaging agents during the treatment of ET. All of our patients with LT received hydroxyurea, a non-alkylating, myelosuppressive agent, in their ET treatment. Hydroxyurea may have contributed to the process of leukemogenesis but it remains difficult to determine the relative contribution of hydroxyurea and ET progression to the leukemogenic process. Leukemic transformation is associated with dismal prognosis. Median survival for patients on supportive treatment was one month. Complete remissions were not durable, with patients eventually relapsing and succumbing to complications of refractory disease. Reported long-term survivors had stem cell transplant either as first therapy or in first CR. More studies are needed to evaluate if this is truly the only successful option.

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