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Research Article

Improved survival in red blood cell transfusion dependent patients with primary myelofibrosis (PMF) receiving iron chelation therapy

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Abstract

Many patients with primary myelofibrosis (PMF) become red blood cell (RBC) transfusion dependent (TD), risking iron overload (IOL). Iron chelation therapy (ICT) may decrease the risk of haemosiderosis associated organ dysfunction, though its benefit in PMF is undefined. To assess the effect of TD and ICT on survival in PMF, we retrospectively reviewed 41 patients. Clinical data were collected from the database and by chart review. The median age at PMF diagnosis was 64 (range 43–86) years. Median white blood cell (WBC) count at diagnosis was 7.6 (range 1.2–70.9) $\times 10^9$/L; haemoglobin 104 (62–145) G/L; platelets 300 (38–2088) $\times 10^9$/L. Lille, Strasser, Mayo and International Prognostic System (IPS) scores were: low risk, $n = 15, 8, 11, 3$; intermediate, $n = 15, 19, 9, 16$; high, $n = 5, 11, 5, 7$; respectively. Primary PMF treatment was: supportive care, $n = 23$; hydroxyurea, $n = 10$; immunomodulatory, $n = 4$; splenectomy, $n = 2$. Sixteen patients were RBC transfusion independent (TI) and 25 TD; of these 10 received ICT for a median of 18.3 (0.1–117) months. Pre-ICT ferritin levels were a median of 2318 (range 263–8400) and at follow up 1571 (1005–3211 μg/L ($p = 0.01$). In an analysis of TD patients, factors significant for overall survival (OS) were: WBC count at diagnosis ($p = 0.002$); monocyte count ($p = 0.0001$); Mayo score ($p = 0.05$); IPS ($p = 0.02$); number of RBC units (NRBCU) transfused ($p = 0.02$) and ICT ($p = 0.003$). In a multivariate analysis, significant factors were: NRBCU ($p = 0.001$) and ICT ($p = 0.0001$). Five year OS for TI, TD-ICT and TD-NO ICT were: 100, 89 and 34%, respectively ($p = 0.003$). The hazard ratio (HR) for receiving >20 RBCU was 7.6 (95% Confidence Intervals [CI] 1.2–49.3) and for ICT was 0.15 (0.03–0.77). In conclusion, 61% of PMF patients developed RBC-TD which portended inferior OS; however patients receiving ICT had comparatively improved OS, suggesting a clinical benefit. Prospective studies of IOL and the impact of ICT in PMF are warranted.

Keywords: myeloproliferative disorder; primary myelofibrosis; transfusion; iron overload; iron chelation therapy

Introduction

Primary myelofibrosis (PMF) is a myeloproliferative disorder characterized by deposition of extracellular matrix in the bone marrow, resulting in marrow fibrosis, angiogenesis and osteosclerosis, and leading to cytopenias and extramedullary haematopoiesis [1,2]. Clinical manifestations of PMF include constitutional symptoms in addition to symptoms from extramedullary haematopoiesis and cytopenias. Current therapies focus on symptom management and optimizing cell counts, and a mainstay of therapy is transfusion support [3]. The only treatment shown to impact upon survival is allogeneic haematopoietic stem cell transplantation, which is generally reserved for young, otherwise healthy individuals because of its significant morbidity and mortality [4,5]; however, the majority of PMF patients are ineligible for this procedure due to age and co-morbidities. Patients with PMF are at risk of progression to acute myeloid leukaemia (AML) [6,7], termed PMF blast phase [2].

Patients with PMF frequently develop anaemia from decreased marrow reserve, splenic sequestration and myelosuppressive medications [3]. Many patients eventually require red blood cell (RBC) transfusions, which may lead to iron overload (IOL) from transfused blood and increased iron absorption [8]; significant IOL may occur after as few as 10–20 RBC units [9], and transfusion dependent (TD) patients may develop cardiac, hepatic and endocrine dysfunction [8,10]. Iron related organ toxicity is mediated in part by deposition of iron into tissues and

organs, and in part by the presence of non-transferrin bound iron (NTBI), which leads to the formation of labile plasma iron (LPI) and reactive oxygen species (ROS) capable of damaging lipids, proteins and nucleic acids, thereby possibly provoking apoptosis [11,12] and mutagenesis [13]. Patients with TD myelodysplastic syndrome (MDS) were shown to have inferior survival to TI patients, with the decrease in survival proportional to the degree of transfusion dependence [14,15], an observation sufficiently significant that it led to the incorporation of transfusion dependence into a new prognostic score [16].

To limit the toxicity of excess iron, patients may receive iron chelation therapy (ICT). The benefits of ICT in patients with thalassaemia major and IOL are well established [17,18] and ICT has been shown to lower LPI levels [19] and reduce oxidative stress [20] in TD patients. More recent studies suggest that administration of ICT may improve survival in patients with MDS and IOL [21,22].

Despite these observations, the role of ICT in PMF remains largely undefined. To assess the effect of transfusion dependence, IOL and ICT on survival in PMF, patients with PMF seen through the Provincial Home Haemosiderosis Program (PHHP) of British Columbia (BC) and at St. Paul's Hospital in Vancouver, Canada were reviewed.

Patients and methods

Patients seen to 2007 with a bone marrow biopsy confirmed diagnosis of PMF were identified from the database of the haematology practice and the PHHP. Patients with another disorder leading to marrow fibrosis were excluded. Clinical features were collected from laboratory records, blood bank records and by chart review.

The PHHP is managed by a single haematologist (L. Vickars) based at St. Paul's Hospital. Until late 2006, the only option for ICT in BC was deferoxamine (DFO) and all patients in the province requiring DFO are referred for assessment and management through the PHHP. With the availability of deferasirox (DFX), management of ICT has shifted to the patients' primary haematologist.

Criteria for initiating ICT were an estimated life expectancy of at least 1–2 years and at least one of: elevated ferritin level (over 1000 μg/L), transfusion of at least 20 RBC units, or organ dysfunction from IOL. DFO was administered 0.5–3 g by subcutaneous infusion over 12 h (dose adjusted to ferritin level), at least 5 days per week. Patients treated with DFX received an initial dose of 20 mg/kg/day, adjusted to transfusion requirements, ferritin level and patient tolerance.

Clinical evidence of IOL was determined retrospectively as organ dysfunction in the absence of other etiology. Cardiac dysfunction was defined as left ventricular enlargement or decreased ejection fraction, clinical signs of systolic or diastolic dysfunction or arrhythmia. Hepatic dysfunction included clinical signs of liver disease or alanine aminotransferase or aspartate aminotransferase greater than 1.5 times the upper limit of normal. Endocrine dysfunction included glucose intolerance or diabetes, and thyroid stimulating hormone level above the upper limit of normal.

A prognostic score was calculated for each patient according to the Lille, Strasser, Mayo and International Prognostic Scoring Systems (IPS) [6,23–25]. IPS intermediate-1 and intermediate-2 risk were combined for analysis.

OS was defined as the time from the date of PMF diagnosis to the date of death from any cause. AML transformation (PMF-BP) was defined as a change in clinical behaviour associated with an increase in circulating blasts in the peripheral blood and/or at least 20% blasts in the bone marrow [26]. Patients still alive were censored at the last known date of follow up. OS was determined by the Kaplan-Meier method and the significance in differences by the log-rank method. Analyses were performed using SPSS for Windows, version 15.0. Survival was compared in subgroups and patient outcomes compared according to clinical and laboratory features.

This study was performed in accordance with the requirements of the St. Paul's Hospital Institutional Research Ethics Board.

Results

Patient characteristics and PMF treatment, including RBC transfusion

Forty one patients with a bone marrow biopsy confirming a diagnosis of PMF were identified. Clinical and laboratory features are summarized in Table 1. Sixteen (39%) patients were TI and 25 (61%) were TD, 10 (24%) of whom received ICT. Median values at diagnosis were: age, 64 (range 43–86) years; WBC, 7.6 (range 1.2–70.9) $\times 10^9$/L; haemoglobin, 104 (62–145) G/L; platelets, 300 (38–2088) $\times 10^9$/L; monocytes, 0.5 (1–5.2) $\times 10^9$/L; LDH ratio (value divided by upper limit of normal), 2.2 (0.5–5.9); circulating blast fraction, 0 (0–5)%; immature granulocyte fraction, 10 (0.2–29.5)% and ferritin level, 201 (57–3300) μg/L. The median distance below the costal margin was for the liver and spleen 2 (0–10) and 5 (0–19) cm, respectively. Specific PMF-directed treatments are shown in Table 1; the majority of patients ($n = 23$, 56%) received supportive care.

The only baseline features that differed between groups were splenomegaly, higher in the TI group ($p = 0.002$); clinical IOL, higher in the ICT group ($p = 0.0001$); and number of RBC units transfused ($p = 0.0001$).

Iron chelation therapy

The median duration of ICT was 18.3 (range 0.1–117) months and reasons for initiating ICT were: number of RBC units (RBCU) received, $n = 9$; elevated ferritin, $n = 6$; clinical IOL, $n = 3$. Five patients received DFO only, four DFX only and one DFO followed by DFX. Reasons for TD patients not undergoing ICT included: received < 20 RBCU, $n = 6$; reason not recorded, $n = 6$; progressed to PMF-BP, $n = 2$; unwilling to subject a

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Table 1. Clinical and laboratory features of 41 patients with PMF according to transfusion dependence and receipt of ICT

Characteristic *n* (%)	Transfusion independent (*n* = 16)	Transfusion dependent, NO ICT (*n* = 15)	Transfusion dependent, receiving ICT (*n* = 10)	*p*
Age (years)				
≤65	8 (50)	8 (53)	7 (70)	NS
>65	8 (50)	7 (47)	3 (30)	
Gender				
Female	6 (38)	3 (20)	3 (30)	NS
Male	10 (62)	12 (80)	7 (70)	
ECOG PS				
0–1	13 (81)	10 (67)	9 (90)	NS
≥2	3 (19)	5 (33)	1 (10)	
WBC count (× 10^9/L)				
<4.0 or >30	5 (31)	3 (20)	0 (0)	NS
4–30	10 (62)	11 (73)	9 (90)	
≤25	12 (75)	12 (80)	9 (90)	
>25	3 (19)	2 (13)	0 (0)	
Haemoglobin (G/L)				
<100	4 (25)	8 (53)	4 (40)	NS
≥100	12 (75)	5 (33)	5 (50)	
Platelet count (× 10^9/L)				
<100	1 (6)	3 (33)	1 (10)	NS
≥100	14 (88)	11 (73)	8 (80)	
Monocyte count (× 10^9/L)				
<1	11 (69)	10 (67)	8 (80)	NS
≥1	4 (25)	3 (20)	0 (0)	
Blast %				
<1	8 (50)	5 (33)	5 (50)	NS
≥1	6 (38)	6 (40)	1 (10)	
Immature granulocyte %				
<10	8 (50)	2 (13)	4 (40)	NS
≥10	4 (25)	9 (60)	2 (20)	
Lactate dehydrogenase				
Normal	3 (19)	1 (6)	3 (30)	NS
Elevated	7 (44)	8 (53)	3 (30)	
Hepatomegaly				
No	6 (38)	5 (33)	4 (40)	NS
Yes	6 (38)	5 (33)	5 (50)	
Splenomegaly				
No	0 (0)	1 (6)	4 (40)	**0.002**
Yes	15 (94)	9 (60)	4 (40)	
Systemic Symptoms				
No	11 (69)	7 (47)	7 (70)	NS
Yes	3 (19)	4 (27)	2 (20)	
Karyotype				
Normal	6 (38)	7 (47)	3 (30)	NS
Abnormal	1[a] (6)	1[b] (7)	1[c] (10)	
Lille prognostic score[d]				
0	6 (38)	4 (27)	5 (50)	NS
1	5 (31)	6 (40)	4 (40)	
2	2 (13)	3 (20)	0 (0)	
Strasser prognostic score[e]				
0	4 (25)	2 (13)	2 (20)	NS
1	10 (62)	4 (27)	5 (50)	
2	2 (13)	7 (47)	2 (20)	
Mayo Prognostic Score[f]				
Low	4 (25)	3 (20)	4 (40)	NS
Intermediate	3 (19)	4 (27)	2 (20)	
High	1 (6)	4 (27)	0 (0)	
IPS[g]				
Low/Intermediate −1 (0–1)	6 (38)	1 (6)	4 (40)	NS
Intermediate - 2/High (>2)	6 (38)	8 (6)	1 (10)	
Primary PMF treatment				
LD chemotherapy[h]	3 (19)	3 (20)	4 (40)	NS
Splenectomy	1 (6)	1 (6)	0 (0)	
Immunomodulatory[i]	1 (6)	1 (6)	2 (20)	
Supportive care	11 (69)	8 (53)	4 (40)	

(*Continues*)

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Table 1. (Continued)

Characteristic *n* (%)	Transfusion independent (*n* = 16)	Transfusion dependent, NO ICT (*n* = 15)	Transfusion dependent, receiving ICT (*n* = 10)	*p*
Ferritin level (μg/L)				
≤1000	5 (31)	2 (13)	5 (50)	NS
>1000	0 (0)	0 (0)	1 (10)	
Clinical IOL[j]				
No	13 (2)	5 (33)	0 (0)	**0.0001**
Yes	1 (6)	10 (66)	10 (100)	
Number of RBC units transfused				
0	16 (100)	0 (0)	0 (0)	**0.0001**
1–20	0 (0)	6 (40)	1 (10)	
21–50	0 (0)	3 (20)	0 (0)	
>50	0 (0)	6 (40)	9 (90)	

[a]tri(14), str12p.
[b]complex.
[c]del(6)(q25).
[d]Dupriez B *et al.*, Blood 1996;88:1013–1018.
[e]Strasser-Weippl K *et al.*, Leuk & Lymph 2006;47(3):441–450.
[f]Tefferi A *et al.*, Cancer 2007;109:2083–2088
[g]Cervantes F *et al.*, Blood 2008;epub ahead of print.
[h]hydroxyurea.
[i]prednisone, *n* = 2; thalidomide, *n* = 1; interferon, *n* = 1.
[j]>20RBC units transfused, *n* = 18; ferritin >1000 μg/L, *n* = 7; CHF, *n* = 5; liver disease, *n* = 3; endocrine, *n* = 3.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICT, iron chelation therapy; IPS, International Prognostic Score; IOL, iron overload; LD, low dose; NS, not significant; *n*, number of patients; PMF, primary myelofibrosis; RBC, red blood cell; WBC, white blood cell.

visually impaired patient to potential ophthalmologic toxicity of ICT, $n = 1$.

PMF-BP progression and overall survival

Median follow up was 61 (0.1–293) months for all patients and 26 (0.1–205), 46 (0.3–244) and 113 (0.1–293) months for TI, TD-NO ICT and TD-ICT respectively. There were no significant differences in the decade of PMF diagnosis between groups (not shown). PMF- BP progression occurred in no TI patients, three TD-NO ICT patients at 21.5, 39 and 101.5 months and one TD-ICT patient at 203 months. All four PMF-BP patients received AML chemotherapy and all died of AML, thus BP-free survival was nearly identical to OS and is not reported further. There were no deaths in TI patients and 13 (52%) deaths in TD patients, two received ICT. Kaplan-Meier analysis showed a median OS for all patients of 126.5 (14.4–293.2) months. OS for TI patients was superior to TD patients (Figure 1). The 5 year OS was 100, 89 and 34% in TI, TD-ICT and TD-NO ICT patients respectively ($p = 0.02$). The median OS for TD-NO ICT patients was 58 months and was not reached for both the TI and TD-ICT patients. In univariate analyses of TD patients, factors significant for OS included WBC count at diagnosis (by both Mayo and IPS criteria); monocyte count; Mayo score; IPS; number of RBC units transfused and receiving ICT ($p < 0.05$ for all). In a multivariate analysis of TD patients, significant factors

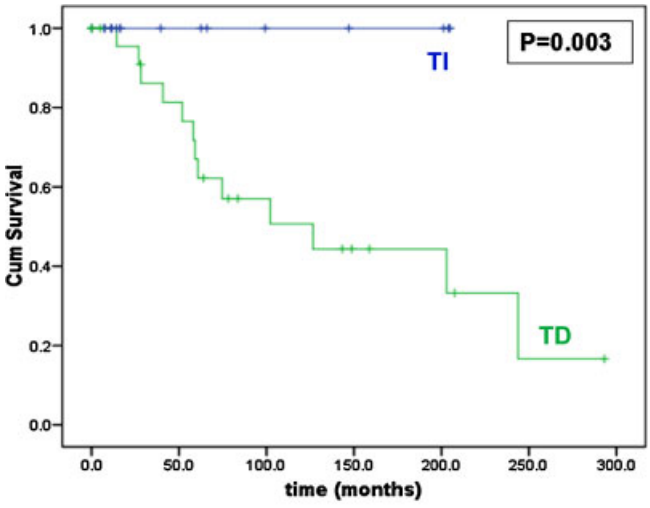

Figure 1. Overall survival in patients with PMF according to transfusion dependence

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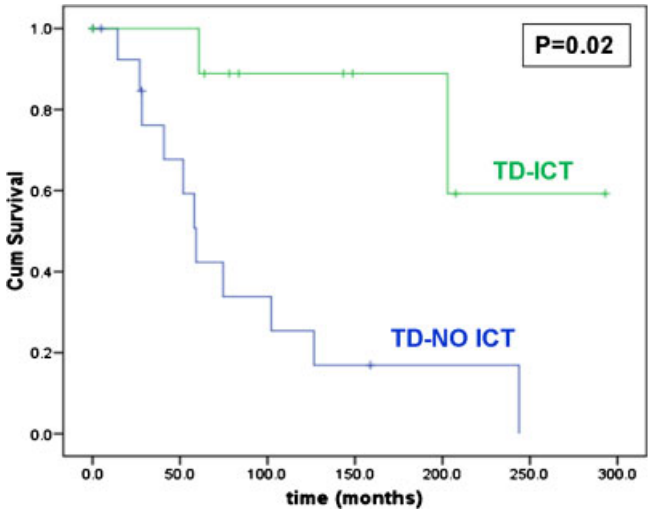

Figure 2. Overall survival in transfusion dependence patients with PMF according to receipt of ICT

were: number of RBC units ($p = 0.003$) and ICT ($p = 0.001$). The HR for receiving >20 RBC units was 7.6 (95% CI 1.2–49.3) and for ICT was 0.15 (0.03–0.77). The OS of TD patients by receipt of ICT is shown in Figure 2. There was no significant difference in OS between the TI and the TD-ICT group (Figure 3).

Causes of the 11 deaths in TD-NO ICT patients were: probably PMF related, $n = 9$ (PMF-BP, $n = 3$; sepsis, $n = 3$; cardiac, $n = 2$; bleeding, $n = 1$) and unknown, $n = 2$. The two deaths in TD-ICT patients were both PMF related: PMF-BP, $n = 1$ and bleeding, $n = 1$ (Table 2).

Ferritin levels

Ferritin levels prior to the initiation of ICT were significantly higher in TD-ICT patients at 2318 (263–8400) μg/L compared to baseline levels of 527 (120–934) μg/L in the TD-NO ICT group ($p = 0.05$). In ICT patients, ferritin levels significantly decreased at follow up to 1571 (1005–3211) μg/L ($p = 0.01$).

Discussion

There has until recently been little data on clinical outcomes in patients with PMF receiving ICT. In this review of the BC provincial experience, transfusion dependence in PMF, as in MDS [27] was associated with inferior survival ($p = 0.02$), and within the TD group, OS was superior in patients receiving ICT ($p = 0.003$). An effect of TD on survival is perhaps not surprising, as multiple prognostic scores for PMF include a haemglobin <10 g/dl as an adverse prognostic factor [6,23–25]. The apparent benefit of ICT suggests, however, that the negative impact of TD, in addition to being a reflection of bone marrow failure, may also be an adverse effect of IOL [11,12].

These data add to observations in MDS and thalassaemia related IOL. That ICT extends the survival of TD thalassaemia patients with IOL is well established [18,28–30]. In MDS, a retrospective study demonstrated that TD patients with low or intermediate-1 IPSS [31] risk

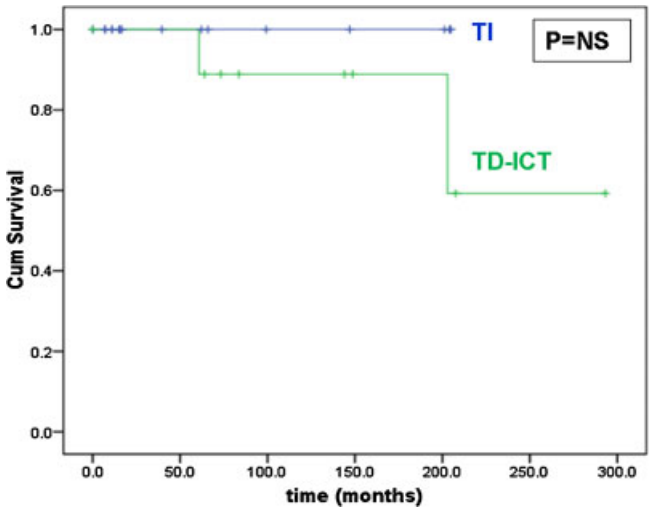

Figure 3. Comparative overall survival of transfusion independent and transfusion dependent-ICT with PMF

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Table 2. Causes of death in PMF patients according to transfusion dependence and receipt of ICT

Causes of death	TI patients (# deaths)	TD-No ICT (# deaths)	TD-ICT (# deaths)
Probably PMF related	0	9	2
PMF-BP	0	3	1
Sepsis	0	3	0
Cardiac	0	2	0
Bleeding	0	1	1
Unknown	0	2	0
Total	0	11	2

Abbreviations: BP, blast phase; ICT, iron chelation therapy; PMF, primary myelofibrosis; TD, transfusion dependent; TI, transfusion independent.

receiving ICT had improved survival compared to similar risk TD patients not receiving ICT ($p = 0.03$) [21], and a second study suggested an ICT dosage effect on survival [22]. It is well documented that TD MDS patients frequently develop IOL related cardiac and hepatic dysfunction [27,32–34], which are often the cause of death [27]. The use of ICT in MDS was recently shown to prevent secondary IOL in TD patients [35], and in thalassaemia related IOL, studies suggest that ICT can at least partially reverse such organ dysfunction and improve survival by preventing the development of organ failure [29,36–38].

As in MDS, PMF patients may be at higher risk for the adverse effects of transfusional haemosiderosis because of co-morbidities associated with ageing. In MDS, the negative effect of TD was seen mainly in lower-risk patients [15]. In the current study, it was not possible to fully evaluate an effect of TD by PMF risk group due to limited patient numbers. However, although prognostic scores could not be calculated in all patients, the median OS for the whole group of 126.5 months suggests that many patients were lower risk; in contrast, in a group of 1054 PMF patients recently reported in whom the risk breakdown was approximately equal, the median OS was 69 months [24]. The Lille prognostic score could be calculated in 36 of 41 patients in this series and was low risk in 15 (42%), corresponding to a median survival in the Lille series of 93 months and 135 months in the IPS. Thus, it seems reasonable to expect that the effect of TD and ICT on clinical outcome might be greater in lower risk PMF.

While it is difficult to be certain retrospectively whether individual deaths were related to toxicity from iron since IOL assessment was made by clinical impression and ferritin levels rather than imaging or biopsy, there was a significant decrease in ferritin levels in ICT patients over the course of the study ($p = 0.01$). Although ferritin is an imperfect reflection of body iron, it has been shown in thalassaemia that maintenance of a serum ferritin level below 2500 μg/L correlates with improved survival [39,40]. A predisposition to infection in IOL has been postulated [41,42], but in PMF and MDS this is difficult to separate from infectious susceptibility due to neutropenia. Recent studies; however, suggest that IOL may contribute to cytopenias by damaging haematopoietic cells [43,44], and in PMF a mitigation of this effect on myelopoiesis by ICT has been reported [45–51]; in theory this effect could contribute to a survival benefit by decreasing infectious episodes. To determine whether there was an effect of IOL or ICT on myelopoiesis in our patients, we examined sequential neutrophil and platelet counts and RBC transfusion requirements and found no significant change (not shown); however, the median duration of ICT was only 18.3 months and patient numbers limited, so an effect on marrow failure could not be fully evaluated. However, in the TD NO-ICT PMF group, there were two deaths from cardiac causes and three from sepsis, while in the ICT group, there were no deaths from either cause, suggesting that IOL related cardiac and haematologic toxicity in the TD NO-ICT patients could have contributed to early mortality. Finally, due to the potentially mutagenic effect of ROS [13], patients with untreated IOL may also be at higher risk for PMF-BP transformation, as has been suggested in MDS [21,52]. PMF-BP transformation occurred in four PMF patients, all TD; three were not receiving ICT. Because of limited numbers and the study's retrospective nature, no definitive conclusions can be drawn regarding IOL directly contributing to death, whether through cardiac or haematologic toxicity or mutagenesis; however, it seems reasonable to postulate that the improvement in survival in ICT patients may have occurred by decreasing the toxic effects of excess iron, as has been demonstrated in thalassaemia and MDS.

The improved survival seen in PMF patients receiving ICT is encouraging. However, because the study is retrospective, it is subject to the potential biases of any analysis that is non-randomized and non-controlled. To minimize the possibility of selection or referral bias favouring ICT patients, multiple baseline characteristics were compared, showing no significant differences between groups in most factors. The majority of patients had a good performance status and received supportive care as primary treatment, providing a relatively homogeneous group in whom the impact of ICT could be followed. However, determination of IOL and predicted life expectancy were not done by a pre-determined set of criteria, although, since the initiation and management of all patients receiving ICT in BC was performed by a single haematologist until DFX became available in late 2006, gross inconsistencies in clinical impression are unlikely. Referral bias favouring ICT patients cannot be ruled out, however, arguing against this, two patients referred for ICT developed PMF-BP

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during the time they waited for a PHHP appointment; the PHHP wait list historically was 12–18 months, and presumably at the time of referral, the referring haematologists judged the patients to have a predicted life expectancy sufficiently long that they could potentially benefit from ICT despite this resource limitation.

The results of this study reinforce transfusion dependence as an adverse prognostic factor in PMF and suggest that in addition to being a marker of marrow failure, TD may contribute to mortality by leading to IOL and its sequelae. These findings are increasingly relevant as PMF therapies which may provide further survival benefit become available [4,5,53–56]. To further clarify the role of ICT in PMF it is important to confirm a beneficial effect in prospective trials. While there are no guidelines for the initiation and use of ICT in PMF, MDS guidelines [57–61] suggest a ferritin level be obtained at diagnosis and regular intervals. Baseline investigations should also include an evaluation of cardiac function [40] and newer modalities, were available, including T2* MRI [37], should be used to objectively document the degree of cardiac and hepatic iron loading, and to assess organ function at standardized intervals. Testing for co-morbid conditions such as viral hepatitis or haemochromatosis [62] may also provide valuable information, and measurement of NTBI, LPI and ROS, were available, would further characterize the impact of iron load on the cellular milieu. Future prospective studies that include these parameters would increase confidence that the improved survival seen in patients receiving ICT is truly related to a decrease in iron burden. Studies are also needed, as in MDS, to evaluate the impact of ICT on patient quality of life [63] and cost/benefit ratio [64].

In conclusion, in this retrospective review of 41 patients with PMF, TD patients had inferior survival, an effect that was mitigated by the use of ICT. The apparent survival benefit provided by ICT in TD PMF warrants further study, particularly now that iron chelators with a convenient formulation are more widely available and other therapies potentially capable of prolonging life in PMF are in clinical development.

Acknowledgements

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