

## Brief Communication

## Prognostic implications of leg ulcers from hydroxycarbamide therapy in patients with essential thrombocythaemia

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## ABSTRACT

Essential thrombocythemia (ET) is a clonal stem-cell disorder characterized by persistent thrombocytosis. Patients with ET and risk factors for thrombotic complications have been shown to benefit from cytoreductive therapy, the most common agent used being, hydroxycarbamide. Although this agent is usually well-tolerated, one of the recognized adverse effects is the development of leg ulcers. We undertook retrospective analysis of consecutive ET patients treated with hydroxycarbamide and identified several specific features for this complication including advanced age, female preponderance, reduced overall survival, tendency to develop future vascular events and intolerance to the second line agent, anagrelide.

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## 1. Introduction

Essential thrombocythemia (ET) is one of the myeloproliferative neoplasms, characterized by a sustained increase in platelet count. The aim of treatment in ET is to reduce the risk of thrombosis, control disease-related symptoms, and to reduce if possible disease progression. The drug of choice for the initial management of ET in most patients (apart from pregnant females) is hydroxycarbamide (HC) [1]. Its principal mode of action is inactivation of ribonucleotide reductase, the enzyme that catalyses the conversion of ribonucleotides to deoxyribonucleotides during *de novo* DNA synthesis. One of the well-recognized adverse effects of HC therapy is the development of leg ulcers. Since there has been no detailed evaluation of this cutaneous side effect from HC therapy, we undertook a retrospective analysis of ET patients who were treated with HC over a fourteen-year period.

## 2. Patient and disease characteristics

Seventy consecutive patients, from a single centre, diagnosed with ET between the years 1986 and 2010 were selected based on the use of HC as their first line treatment. The average age at diagnosis was 64.8 years (range 36–87 years). This included 36 females and 34 males. 34 patients (49%) were JAK-2 positive, 30 patients (43%)

were JAK-2 negative, 5 patients (7%) MPL positive and 1 patient (1%) both MPL and JAK2 positive. 40 patients (57%) were diagnosed after noticing a high platelet count following a routine full blood count. 30 patients (43%) presented with symptoms of micro-vascular disturbances including headaches, transient ischaemic attacks or erythromelalgia. Bone marrow histology revealed 12 patients (17%) to have grade 3 fibrosis, 20 patients (28.6%) grade 2 fibrosis, 23 patients (32.9%) grade 1 fibrosis and 15 patients had no fibrosis.

## 3. Results

Eleven out of the seventy patients (15.7%) developed leg ulcers while on treatment with HC. The average age of patients developing leg ulcers was 72 years at diagnosis (range 65–80 years), compared with an average age of 63.5 years for non-leg ulcer patients ( $p = 0.004$ ). There was a predominance of females in the group who developed leg ulcers (eight versus three). Also while all the three males developed grade 1 leg ulcers, four female patients had grade 3 and another four grade 2 leg ulcers (grade 1 – red non blanching erythematous area only, grade 2 – partial thickness wounds with damage to epidermis and/or dermis, grade 3 – full thickness wounds with necrosis of epidermis/dermis and subcutaneous extension and grade 4 – exposure of muscle or bone).

Out of the eleven patients, four had a documented history of venous insufficiency of the same leg, the ulcer occurred, and two patients had a history of diabetes mellitus and hypertension. All the eleven patients developed leg ulcers on either the medial or lateral malleolus. Seven of them had solitary ulcers over the lateral

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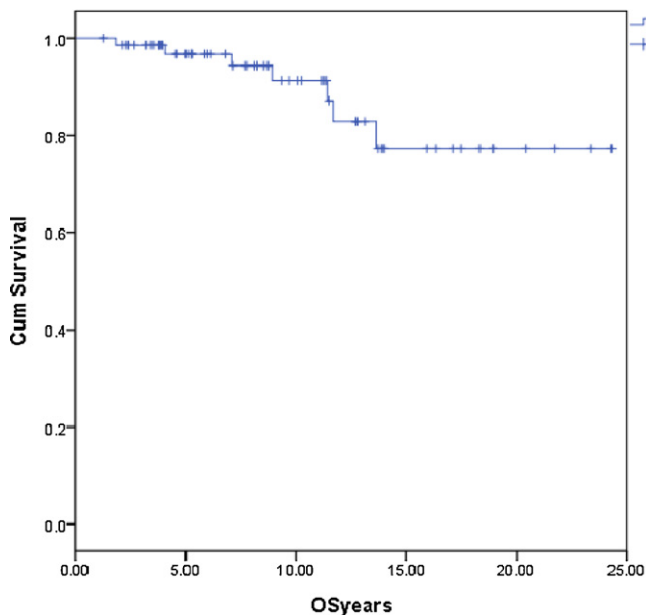


Fig. 1. Overall survival of all patients with essential thrombocythaemia.

malleolus, while four developed multiple, small circular on both malleoli.

The average length of time from HC initiation to development of leg ulcers was 2.1 years (range 0.5 months–6 years). The average dose of HC in the leg ulcer group was 780 mg, while the average dose in the non leg ulcer group was 760 mg. The average mean red cell volume (MCV) of patients who developed leg ulcers was 117.6 fl, while in the rest of the group, the average MCV was 114.2 fl. Since both HC therapy and the underlying myeloproliferative neoplasm can predispose to other skin disorders like pyoderma gangrenosum and squamous cell carcinoma [2], we undertook skin biopsies of the recent patients. This confirmed the epidermal atrophy, dermal fibrosis, and scar tissue without vascular lesion usually described with leg ulcers secondary to HC treatment [3]. In all the cases, the leg ulcers resolved after stopping the HC. The average length of time for the ulcers to heal was 8.6 months, with grade 3 leg ulcers taking more time to resolve.

Seven patients out of the seventy patients (10%) had died during the time period studied. Fig. 1 shows the overall survival for the whole group. Of these seven patients, six had developed leg ulcers suggesting that the overall survival is significantly reduced in those patients who develop leg ulcers on HC therapy (Fig. 2). Three patients died of myocardial infarction while another died of pneumonia. The length of time between leg ulcer development and death from cardiac episodes was 2.61 years (range 2.5–2.8 years).

Next we compared the incidence of leg ulcers with cytopenias, another well-recognized side effect of HC. For the purpose of the study, cytopenia was arbitrarily defined as haemoglobin less than 10 g/dl, neutrophil count less than  $1.5 \times 10^9/L$  and platelet count less than  $100 \times 10^9/L$ . Forty out of seventy patients (57%) developed some form of cytopenia, of which thirty-five patients (50%) were over sixty-five years old. Although this difference was statistically significant ( $p=0.01$ ; chi square test), patients who developed cytopenia did not have a reduced overall survival ( $p=0.82$ ).

Follow-up of patients who discontinued HC due to adverse effects also revealed some interesting findings. Out of a total of twenty-six patients (37.1%) who needed to discontinue HC, sixteen patients were switched to anagrelide. The reasons for HC discontinuation was leg ulcers (11 patients), cytopenia (7 patients), refractoriness to HC (4 patients), and progression to

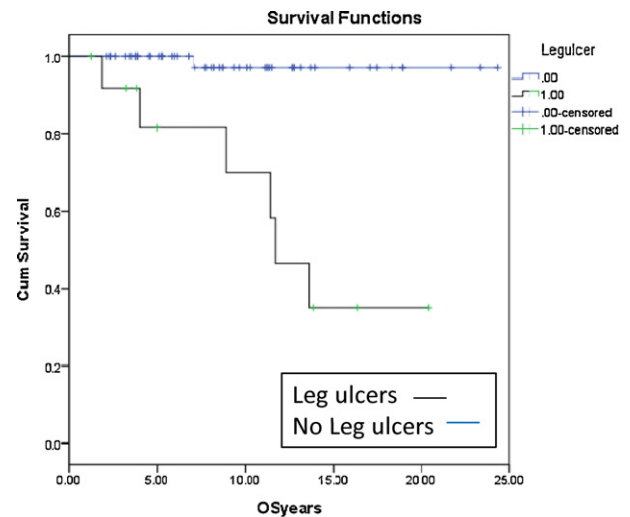


Fig. 2. Overall survival for patients with essential thrombocythaemia who developed leg ulcers after treatment with hydroxycarbamide compared with those who did not.

myelodysplastic syndrome and myelofibrosis (2 patients each). Surprisingly, nine out of the sixteen patients who were commenced on anagrelide were found to be intolerant of this treatment. The reasons for anagrelide intolerance were palpitations (4 patients), development of cardiac arrhythmia, congestive cardiac failure, rash and severe headaches (1 patient each) and refractoriness in one patient. Of the 11 patients who had leg ulcers, 4 were intolerant to anagrelide. The intolerances were due to symptoms of CCF (3 pts) and 1 patient was resistant to anagrelide.

#### 4. Discussion

Leg ulcers as the cutaneous adverse effect of HC treatment is well-known although clinical and prognostic correlates of this unusual side effect has not been previously studied. Although the exact mechanism for the development of this complication is still unclear, it has been hypothesized that inadvertent minor injury to the malleolar region may not be adequately repaired due to the drugs negative effect on the regenerative potential of the epidermis [4]. Although a lag of up to five years on average for leg ulcer development with HC has been noted [5], the present study noted much earlier (2.1 years) onset. This considerable period of exposure to the drug before ulcer formation, chronic and slow ulcer enlargement, and healing after discontinuation suggest a cumulative toxic effect of the medication [6].

The risk factors for developing leg ulcers with HC have previously been considered. One of the points raised in previous reports has been an increased MCV [7]. Macrocytic red cells or erythroblasts have impaired deformability making them circulate poorly through the capillary network. This can also lead to anoxia causing the characteristic painful leg ulcers. Although there was no statistically significant difference between the MCV in the leg ulcer group and non leg ulcer group in our study, the patients with leg ulcers did have a slightly higher MCV.

It was also interesting to note that four of the eleven patients who developed leg ulcers had venous insufficiency and two others had risk factors for vascular disease. Bader and colleagues [4] also noted that all the ulcers observed in their patients also occurred in a leg with superficial or deep venous insufficiency. Since altered microcirculation is known to occur in ET giving rise to erythromelalgia and raynauds phenomenon, a careful assessment of the peripheral circulation may be warranted in patients with these symptoms before commencement of HC, if possible. This

recommendation is not without issues since HC is started in ET patients with cardiovascular risk factors and detailed evaluation of all patients may not be practical.

Our study noted a female preponderance for developing leg ulcers in more severe forms. Ruzzon et al. also noted that of the 5 patients who developed leg ulcers, in their study cohort of 124 myeloproliferative patients on hydroxycarbamide, all were female [8]. This sex difference may be explained by the lack of beneficial effects oestrogen has on the skin in older females. Oestrogen acts on multiple cell types in the wound to modulate the healing process. It impairs neutrophil chemotaxis, reduces release of pro-inflammatory cytokines and is mitogenic for keratinocytes, accelerating re-epithelialization [9]. In normal unwounded skin, topical oestrogen treatment reverses skin atrophy, improves skin dryness and wrinkles by increasing dermal water holding capacity [10]. Oestrogen creams have been reported to be beneficial in leg ulcer [11].

Probably the most surprising and significant finding from our analysis was the correlation of poor survival with leg ulcers in patients on HC therapy. This is most likely due to the underlying vasculopathy which has predisposed these individuals to the development of the skin complication. In support of this hypothesis, a recent report have suggested leg ulcer in sickle cell disease as a marker of vasculopathy [12]. A study of ninety-four sickle cell disease patients who suffered leg ulcers demonstrated lower pulse oximetry, higher tricuspid regurgitation velocities, serum uric acid and serum brain natriuretic peptide. The authors concluded that patients with leg ulceration are at risk to develop serious vascular complications of sickle cell disease, such as pulmonary hypertension, priapism and, possibly, renal disease. In our study, although only includes a small number of patients, three died from a cardiac event while the retrospective analysis limited identification of cardiovascular status of the other three patients who died from pneumonia. The 'vasculopathic' status of leg ulcer patients may also explain the cardiac side effects from anagrelide in the same patients. It may be recommended that patients who develop leg ulcers from HC should only be switched to anagrelide therapy after a full work-up to exclude cardiovascular pathology is undertaken. The incidence of side effects when switching from Hydroxycarbamide to Anagrelide seems to be significant with 9 out of 16 patients experiencing complications. This contrasts to previous studies which shows first line treatment with anagrelide, in Essential Thrombocythaemia, has mild cardiovascular adverse effects [13].

Although our analysis of leg ulcer patients in ET is the first of its kind, there are limitations in the analysis due to the retrospective nature and small number of patients who developed leg ulcers. However, the study provides some useful guidance on the relationship of leg ulcer development in patients on HC therapy suggesting

careful assessment for cardiovascular problems in these patients and before switching to anagrelide therapy.

### Authors' contribution

SF: provided the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article; DB: provided the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article; CB: acquisition of data; JT: analysis and interpretation of data, and drafting the article.

### Conflict of interest

All authors have no conflict of interest to report.

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