below the mean BMD in young adults (20–40 years old) of the same gender. The *Z*-score denotes how many SDs a person's BMD is above or below the mean BMD in the matched population. The coefficient of variation (CV) for the areal BMD measurements ranged from 0.5 to 3%, depending on application.

*Peripheral quantitative computerized tomography.* The volumetric BMD ($g/cm^3$) of the nondominant distal arm (the radial bone) and distal leg (the tibial bone) was measured by pQCT (XCT-2000, Stratec Medizintechnik, GmbH, Pforzheim, Germany). The pQCT-device was calibrated once a week using a standard phantom and once every 30 day using a cone phantom provided by the manufacturer. A 2-mm-thick single tomographic slice was scanned with a voxel size of 0.50 mm. The cortical volumetric BMD was measured using a scan through the diaphysis at 25% of the bone length in the proximal direction of the distal end of the radial and tibial bones, respectively. Trabecular volumetric BMD was measured using a scan through the metaphysis at 4% of the bone length in the proximal direction of the distal end of the radial and tibial bones, respectively. All pQCT analyses were performed by a single technician using a single pQCT device. The CVs were less than 1% for all pQCT measurements, as previously reported [25].

*Statistics.* Paired two-sided *t*-tests and Wilcoxon signed rank tests were performed to evaluate differences over time in each group. Unpaired two-sided *t*-tests and Mann–Whitney *U* were performed to compare CML patients and controls. Fischer's exact test was used to compare the number of individuals with hyperparathyroidism in 2007 and 2011, respectively. A $P < 0.05$ was considered statistically significant. All data shown are mean values ± standard error of mean (SEM) unless otherwise stated.

### Author Contributions

Sofia Jönsson, Hans Wadenvik, Dan Mellström designed the study. Sofia Jönsson and Hans Wadenvik recruited the study patients and controls. Sofia Jönsson collected the data. Sofia Jönsson, Hans Wadenvik, Therese Standal, and Bob Olsson wrote the article.

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# Hydroxyurea-related toxicity in 3,411 patients with Ph'-negative MPN

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**Hydroxyurea (Hydroxycarbamide; HU) is commonly used for the long-term treatment of patients with Philadelphia-chromosome negative chronic myeloproliferative neoplasms (MPNs). It is considered a first-choice agent for the treatment of these disorders as underlined by the European Leukemia Net Consensus Conference [1], although it is formally approved for this indication in some countries only. The drug is reportedly well tolerated in the large majority of subjects, although systemic and/or localized toxicities have been reported. Consensus criteria for definition of "intolerance" to HU have been described; patients who develop intolerance are candidate for second-line therapy**

**and, more recently, for investigational drugs. However, no epidemiologic information about the occurrence of the most clinically significant HU-associated adverse events is yet available. In this study, the authors report on a multicenter series of 3,411 patients who were treated with HU among which 184, accounting for 5% of total, developed significant drug-related toxicities. These data provide an estimate of the frequency and a detailed characterization of clinically significant HU-related toxicities; these information have relevance for the management of MPN patients who require second-line therapy after developing HU-related intolerance.**

Hydroxyurea (HU) is a widely used anticancer agent belonging to the family of antimetabolites; mechanism of action is ascribed to reduction of deoxyribonucleotide production via inhibition of the enzyme ribonucleotide reductase through scavenging of tyrosyl-free radicals [2]. The effectiveness of HU in controlling MPN signs and symptoms is documented by two randomized trials in patients with high-risk essential thrombocythemia (ET) where the drug was compared with placebo (the "Bergamo" trial) [3] or anagrelide (the PT-1 study) [4]. Although no controlled study has been performed yet in polycythemia vera (PV), early reports from the Polycythemia Vera Study Group in 1980s indicated the superiority of HU when compared with phlebotomies in the prevention of cardiovascular events and evolution to myelofibrosis (MF). HU is used also for the treatment of splenomegaly and myeloproliferation signs and symptoms in primary MF (PMF); in an uncontrolled, single center study [5] up to 40% of the patients achieved clinical improvement according to the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria [6], although responses were of short duration.

HU is well tolerated in most patients who have been receiving the drug for a long-period of time. Most common, low-grade side effects are represented by gastrointestinal complains, such as nausea, gastric intolerance, diarrhea; they are all usually transient and occur at the highest doses. The increased red cell corpuscular volume that occurs during treatment has no clinical relevance and does not require vitamin supplementation. However, a minority of the patients develop other more severe systemic symptoms and cutaneous manifestations that require either dose reduction at dosage that eventually results in unsatisfactory control of disease manifestations or switch to second-line therapies. Criteria for definition of "intolerance" (and/or "resistance") to HU in the settings of ET [7], PV and MF [8] have been developed by the European Leukemia Net (ELN) in an expert consensus statement. The ELN criteria of intolerance (and resistance) to HU are currently used as enrolling criteria for clinical trials with novel drugs, including JAK2 inhibitors [9] and histone deacetylase inhibitors [10]. However, information about rate of occurrence and clinical correlates of ELN-defined unacceptable HU toxicity are limited to anecdotal cases or very small series; a large study focusing only on cutaneous toxicity has been published recently.

In this retrospective study, the authors collected data from a large multicenter series of patients with MPNs with the aim to estimate the frequency and clarify the clinical relevance of unacceptable side effects (fever, pneumonitis, and cutaneous or mucosal lesions) during treatment with HU. Due to the large subjectivity of reporting, the authors deliberately excluded from the analysis gastrointestinal toxicities, even if they were considered as drug-related in patients' and/or physicians' opinion.

The whole study population included 3,411 MPN patients treated with HU, 963 PV, 1912 ET, 357 PMF, 93 PPV, and 86 PET, diagnosed in the contributing centers in the period from 1980 to 2010. One hundred eighty-four patients (5%) developed HU side effects: 16 fever, 167 mucocutaneous lesion(s) and 1 pneumonitis; their characteristics are reported in Table I. In 166 patients (90%), HU was used as first-line therapy.

**TABLE I. Characteristics of the Patients Who Developed HU-Related Side Effects**

| | PV ($n$ = 61) | ET ($n$ = 97) | MF ($n$ = 26) |
|---|---|---|---|
| M/F | 26/35 | 38/59 | 8/18 |
| Median age, range (years) | 65 (40–82) | 64 (19–85) | 68 (31–81) |
| *JAK2*V617F mutated, *N* (%) | 48/48 (98) | 50/82 (62) | 15/22 (69) |
| Other therapies before HU, *N* (%) | 7 (11) | 7 (7) | 4 (16) |
| Side effects | | | |
| Fever, *N* (%) | 4 (6) | 11 (11) | 1 (4) |
| Pneumonitis, *N* | – | – | 1 |
| Ulcers, *N* (%) | 57 (94) | 86 (88) | 24 (96) |

*Fever.* HU-related fever (>38.5°C) developed in 4 PV, 11 ET, and 1 MF patients; median age 64 years (range 50–79 years), 8 were males, 14 were *JAK2*V617F mutated. Fever was reported after a median of 31 days (range 1–109) of treatment at a median dosage of 0.5 g/die (range 0.15–1 g) and a total median dose of 15 g (range 0.5–52.5 g). Physical examination, blood and urine cultures, radiology investigations were routinely negative, neither allergy history nor evidence of immunodepression was found; all had received HU as first agent. Fever resolved spontaneously after HU discontinuation in all patients; in two cases where the drug was reintroduced later on, fever reappeared soon. Presently, all patients are under treatment with alternative drugs (busulfan, anagrelide, pipobroman, or JAK2 inhibitors) without side effects. Less than 30 cases of HU-induced fever have been reported in the literature. Diagnosis was presumptive, based by resolution of fever after HU withdrawal and its recurrence after re-challenge. The pathogenesis remains unclear.

*Pneumonitis.* Pulmonary toxicity related to HU was diagnosed in one patient, a 68-year-old male with *JAK2*V617F negative PMF diagnosed since 10 years and treated with 1 g daily HU (cumulative dose, 3,530 g.). He referred sudden breathlessness without fever; a chest radiography demonstrated diffuse heterogeneous opacities and high resolution lung CT scan showed traction bronchiectasis without honey combing or ground glass infiltrates. Histopatholoy of lung biopsy was characterized by areas of interstitial fibrosis with reactive alveolar macrophages. HU was interrupted with rapid improvement of pulmonary manifestations. HU-induced lung disease has been described in only few cases of patients with MPN disease; it might be misinterpreted as bacterial pneumonia because of nonspecific pathological and histological findings.

*Ulcers.* Mucocutaneous lesions were diagnosed in 167 patients. Twenty-eight patients presented mucosal lesions (17%), 118 (71%) had cutaneous ulcers, and 21 (12%) developed other cutaneous toxicities including keratosis, dyschromia, basalioma, and dermatitis; two patients reported both mucosal and cutaneous lesions (Table II).

Mucosal lesions were more frequent in females (62%), mostly in the oral cavity (96%), and were characterized by pain, burning sensation, and in few patients by weight loss and teeth decay. Mucosal biopsy, performed in only two cases, yielded a no-specific flogistic reaction. In 13 patients (46%) HU was interrupted with resolution of lesions in about one month; the remaining received local therapy using mouthwash with folic acid and vitamin A, obtaining

**TABLE II. Characteristics of HU-Related Mucocutaneous Lesions**

| | Mucosal lesions | Cutaneous ulcers | Other cutaneous lesions |
|---|---|---|---|
| Patients, *n* | 28 | 118 | 21 |
| M/F | 4/24 | 46/72 | 13/8 |
| Age (years) median | 60 (19–76) | 66 (23–85) | 63 (38–81) |
| Disease | PV = 11; ET = 17; MF = 0 | PV = 35; ET = 61; MF = 22 | PV = 11; ET = 8; MF = 2 |
| *JAK2*V617F pos, *N* (%) | 19/23 (83) | 70/97 (72) | 11/17 (65) |
| Previous therapy | Interferon = 1; Anagrelide = 2 | Pipobroman = 7; Interferon = 2; Busulfan = 3; Others = 3 | No |
| Site | Oral = 27; Genital = 1 | Foot/ankle = 15; Malleolus = 58; Leg = 38; Other = 7 | Keratosis = 7; Dyschromia = 7; Dermatitis = 4; Basalioma = 3 |
| HU median daily dose, g (range) | 1 (0.5–5) | 1 (0.25–2) | 1 (0.15–1) |
| HU total dose for patient, g (range) | 1,157 (41–6,940) | 1,947 (12–9,483) | 1,356 (54–4,368) |
| Median time on HU, months (range) | 41 (1–231) | 78 (2–262) | 60 (5–221) |

some symptomatic improvement. However, complete recovery was achieved only after HU dose reduction or suspension in a median of 3 months.

Cutaneous ulcers attributed to HU were recorded in 118 patients, 72 females (61%) and 46 males; 61 ET (52%), 35 PV (30%) and 22 MF (18%). Ulcers were found in the perimalleolar region in 64 patients (54%), the pretibial area in 38 (32%), and on feet, hands and face in 11 (9%); in 20 (17%) patients ulcers were bilateral. Typically lesions were extremely painful, and caused difficulty in deambulation in some patients. Peri-ulcerous skin was thin and erythematous, occasionally necrotic or purulent. In four patients in whom biopsy was performed histological diagnosis was of panniculitis with venous vessel ectasia and inflammation, often accompanied by reduction of elastic fibers. In 62 patients (52%) at least one concurrent risk factor was identified: arterial hypertension (21), peripheral vascular disease (18), diabetes (4); two different risk factors were present in 14 patients, while in five cases a local trauma shortly preceded the lesion. Fifteen patients (13%) had been previously treated with other cytoreductive drugs. In 87 patients (74%), treatment with HU was stopped and switched to other cytoreductive drugs. A complete wound healing was obtained in 53 patients (61%) in a median of 5 months (range 1–28), following withdrawal of HU and concurrent use of therapeutic strategies such as decompression chamber, wounds surgical toilettes, local therapy with antibiotics and heparin. The lesions reappeared in 7 of 14 patients in whom HU was reintroduced after ulcer healing. Thirty-one patients continued to assume HU at a reduced dosage; in 8 (26%) some improvement of ulcer without healing was reported over several months. In a single case, leg amputation was needed for ulcer worsening and local infection.

Dysplastic precarcinomatous lesions (actinic keratosis) were found in seven patients (three were females): 5 PV, 1 ET, 1 PMF, median age 65 (range 58–81), after a median period of 46 months (range 5–148) of HU treatment at a median dosage of 1 g/die (range 0.35–1), and a total HU median exposure of 1,388 g (range 54–4,368 g). Three patients temporarily interrupted or reduced HU treatment with an improvement of lesions but no complete resolution; in the four patients who continued HU worsening of lesions was reported in one and transformation to squamous cell carcinoma occurred in three. Basalioma was diagnosed by skin biopsy in three patients: two PV males and one ET female, median age 66 years, no previous exposure to cytoreductive drugs, after a median time of HU exposition of 60 months, a median daily dose of 500 mg and cumulative exposure of 1,318 g (range 270–1,327). Lesions were treated surgically; treatment with HU was continued in two patients who are still in follow-up without evidence of recurrence after a median of 12 months.

Other adverse cutaneous effects, dyschromic lesions, and dermatitis, were reported by 11 patients (four PV, six ET, ome PET-MF), localized on the face, hands, and feet. Median daily dose was 1 g, median exposure 72 months (range 20–221), and cumulative dose 1,621 g (range 605–3,716 g). All patients stopped HU with rapid resolution of the lesions.

In conclusion, results from this large study indicate that clinically relevant toxicities attributed to HU, in accordance with the criteria of "intolerance" established by the ELN consensus conference, occur in a small proportion of patients even after long exposure time. The rate of 5% discontinuation in this retrospective study is lower than the 10.6% found in the HU plus aspirin group ($n = 404$) of the PT-1 trial [4]; however, in the latter study no detailed information about causes of discontinuation were reported, and it is possible that also gastrointestinal side effects, that have not been considered in our study, were included. Patients who develop severe HU-related toxicities represent a category of subjects in need of alternative therapies.

## Patients and Methods

This study was promoted by the AGIMM group (http://www.progettooagimm.it) and performed with the contribution of additional Italian Centers reporting to the MPN Working Party of the GIMEMA (Italian Group for Malignant Hematologic disorders of the Adult). In total, 10 tertiary centers with long-standing experience in MPN and an available clinical database participated to this retrospective study. The study group was represented by patients listed in the center database who developed a severe side effect related to HU: fever, pneumonitis, and mucocutaneous lesions. For epidemiology and comparison purposes, each center was asked to provide the total number of patients with MPN diagnosis who had been in treatment with HU in the same period of time without developing side effects. Thus, the whole patient study cohort was comprised of 3,411 patients with MPN who had received HU.

Diagnostic criteria for PV, ET, or primary myelofibrosis (PMF) were those of the WHO2008 [11], the PVSG/WHO2001 [12], and the Italian Consensus Conference for Myelofibrosis [13], depending on the period of diagnosis, while for post-PV or post-ET myelofibrosis (MF) a diagnosis according to the IWG-MTR plus the histological WHO criteria was required [14].

The study was approved by referring IRB and was conform to the Declaration of Helsinki on medical research in humans.

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