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# Hydroxycarbamide: a user's guide for chronic myeloproliferative disorders

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Hydroxycarbamide is a nonalkylating antiproliferative and antiviral agent that has been used for over 40 years to treat a variety of neoplastic and non-neoplastic conditions. Hydroxycarbamide is readily absorbed and widely distributed throughout the body. It acts primarily to inhibit DNA synthesis, which underpins its use in solid tumors, viral infections and chronic myeloproliferative disorders. Hydroxycarbamide is an effective treatment for preventing transient ischemic attacks associated with thrombocytosis in chronic myeloproliferative disorders because it is a nitric oxide donor. While its mechanism of action and side-effect profile are well defined, its potential for leukemic transformation as a single agent is still a matter of controversy. Based on a search of the Medline database, this article encompasses the pharmacokinetics, pharmacodynamics, clinical use and tolerability of hydroxycarbamide, plus its potential for mutagenicity with special reference to the chronic myeloproliferative disorders. The toxicity profile of hydroxycarbamide is also discussed to enable clinicians to balance potential risks with therapeutic benefits.

**KEYWORDS:** acute leukemia • essential thrombocythemia • hydroxycarbamide • polycythemia vera

Hydroxycarbamide, also known as hydroxyurea, is a nonalkylating antineoplastic and antiviral hydroxylated urea analog (FIGURE 1) that has been used for a variety of conditions in the disciplines of hematology, oncology and infectious disease. Originally synthesized by Dressler and Stein in 1869 [1], it was not until 1928 that the biological effects of this chemically simple antimetabolite were determined [2].

Hydroxycarbamide's effectiveness as an anti-neoplastic drug was first demonstrated in clinical trials in the 1960s [3,4], and it was subsequently used to treat primary brain cancer, renal cell carcinoma, head and neck cancers, melanoma, and breast cancer [5,6]. The therapeutic spectrum for hydroxycarbamide expanded in the 1980s to include the chronic myeloproliferative disorders (MPDs), polycythemia vera (PV), essential thrombocythemia (ET), chronic myeloid leukemia (CML), hypereosinophilic syndrome (HES) and primary myelofibrosis (PMF), for all of which it is still used.

Hydroxycarbamide is now an established, reliable agent for use in neoplastic and non-neoplastic disorders. However, despite the evidence of its clinical efficacy in a range of disorders, because of the advent of newer agents and concern regarding its mutagenicity, hydroxycarbamide has in

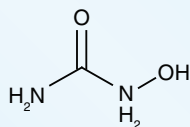
some instances been replaced by other therapies but still remains a staple in the management of chronic MPDs. This article summarizes the pharmacokinetics and pharmacodynamics of hydroxycarbamide and surveys its therapeutic use in the chronic myeloproliferative disorders. The toxicity profile of hydroxycarbamide is also discussed to enable clinicians to balance its potential risks with its therapeutic benefits.

## Methods

Relevant English language articles reporting on basic science, pharmacology, clinical trials, reviews, case series, case reports and abstracts were identified via searches of Medline for all years, using the search terms 'hydroxycarbamide', 'hydroxyurea', 'cytoreductive therapy and chronic myeloproliferative disorders', 'polycythemia vera', 'essential thrombocytosis', 'primary myelofibrosis' and 'chronic myelogenous leukemia'. The reference lists of the identified articles were also searched for additional relevant publications.

## Pharmacokinetics

Hydroxycarbamide is readily absorbed from the GI tract, reaching peak blood levels 1–2 h after ingestion (FIGURE 2), with a bioavailability of almost



**Figure 1. Hydroxycarbamide.**

100%, rendering an intravenous formulation unnecessary under normal circumstances [7]. Owing to its water solubility, hydroxycarbamide enters cells via passive diffusion, and as such, gloves should be worn when handling the drug. Hydroxycarbamide rapidly equilibrates between plasma and body tissues, resulting in a distribution volume equivalent to total body water [8]. Hydroxycarbamide is, therefore, widely distributed throughout the body and, owing to its ability to cross the blood–brain barrier, in the CNS; it also crosses the placenta and is present in breast milk. In contrast to other oral chemotherapeutic agents such as busulfan, interindividual variability with respect to bioavailability and pharmacokinetics is low [7]. With a half-life of 3–4 h, hydroxycarbamide is rapidly excreted from the body via both renal and nonrenal (primarily hepatic) routes with both linear and nonlinear kinetics [7,8]. Renal insufficiency (creatinine clearance <60 ml/min) is an indication to reduce the hydroxycarbamide dose by 50% [9].

### Pharmacodynamics

Hydroxycarbamide is a cytostatic agent that has a common effect in all cells during DNA synthesis, which is most obvious in tissues with a high cell turnover (e.g., hematopoietic tissue, oral and

gastrointestinal mucosa and skin). Its principal mode of action is inactivation of ribonucleotide reductase (FIGURE 3), the enzyme that catalyses the conversion of ribonucleotides to deoxyribonucleotides during *de novo* DNA synthesis, the rate-limiting step in this process [8,10,11]. Ribonucleotide reductase is composed of two subunits, R1 and R2; R1 contains binding sites for substrates and allosteric effectors, while the smaller R2 subunit contains a nonheme iron and a tyrosyl free radical that are essential for enzymatic activity. Hydroxycarbamide selectively quenches the tyrosyl free radical, inhibiting reductase activity. Inhibition of ribonucleotide reductase results in cessation of DNA synthesis, death of S-phase cells [12], and synchronization of surviving cells [13]. As corollaries, iron chelation also causes loss of enzymatic activity, while ribonucleotide reductase gene amplification enhances malignant potential. Hydroxycarbamide induces apoptosis [14] and enhances histone deacetylase inhibitor (HDACi)-induced apoptosis [15] when administered together, an effect mediated via hydroxycarbamide-induced degradation of the cyclin-dependent kinase inhibitors p21 and p27, which compete for binding to caspase 3 [15]. Through depletion of the deoxyribonucleotide cellular pool, hydroxycarbamide also enhances the activity of pyrimidine and purine antimetabolites used for the treatment of some cancers [16].

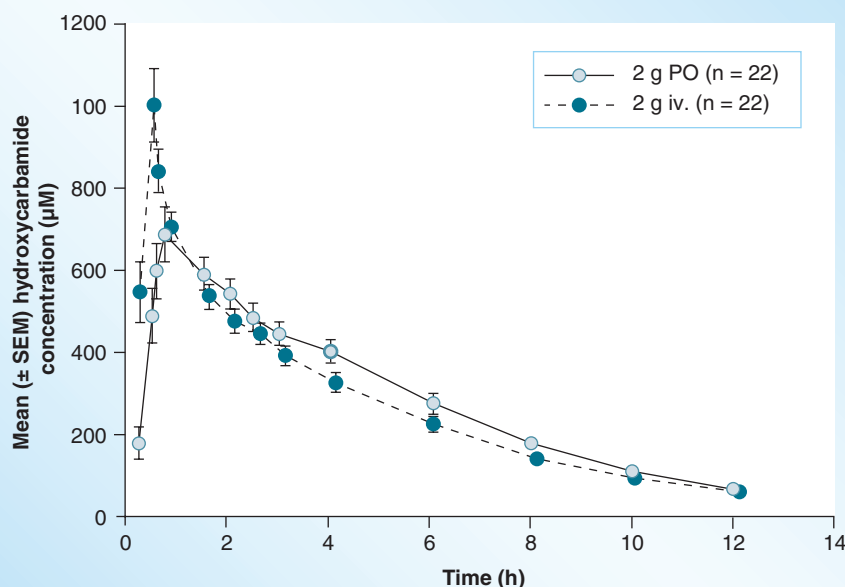
In addition, hydroxycarbamide has the potential to sensitize tumors to other chemotherapeutic agents [17]. Importantly, arrest of DNA replication by hydroxycarbamide can lead to dsDNA breaks, the repair of which may be inhibited because the enzyme complex involved in DNA repair is the same as that involved in DNA replication [17]. Continuous exposure to hydroxycarbamide also leads to accelerated loss of extrachromosomal-amplified genes. As these genes are responsible for the development of resistance to some anticancer agents, hydroxycarbamide could potentially

be useful to reverse acquired resistance to chemotherapy [8].

Nitric oxide free radicals released during hydroxycarbamide metabolism elicit vasodilation, which may explain its ability to prevent transient ischemic attacks in PV and ET patients [18] and also increase red blood cell fetal hemoglobin levels [19].

### Clinical uses of hydroxycarbamide *Myeloproliferative disorders*

Hydroxycarbamide has been used to control the blood counts in CML, HES and the chronic MPD, PV, ET and PMF (the features common to the chronic MPD are summarized in Box 1). In current practice, targeted therapies such as imatinib, dasatinib and nilotinib have supplanted the use of hydroxycarbamide in CML [20], except when there is a need for immediate suppression of myelopoiesis while these drugs are taking effect [21]. Anagrelide is also effective for platelet count suppression in symptomatic, hydroxycarbamide-refractory CML



**Figure 2. Plasma concentration versus time for oral and intravenous administration of hydroxycarbamide.**

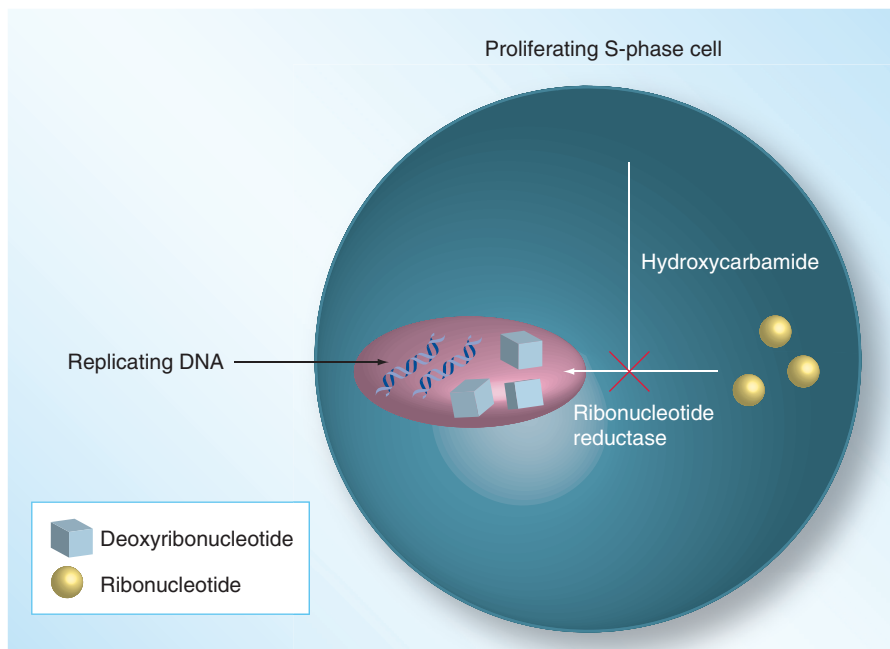
iv.: Intravenous; SEM: Standard error of the mean. Redrawn with permission from [7].

patients [22]. In HES, imatinib and IFN- $\alpha$  have largely replaced hydroxycarbamide; however, not all patients respond to these agents, and in such cases hydroxycarbamide is still useful [23]. Hydroxycarbamide is also currently used as palliative therapy for elderly acute myelogenous leukemia patients who are not candidates for intensive chemotherapy.

With respect to chronic MPD, because it was unequivocally demonstrated that alkylating agents and radioactive phosphorous, once widely used in their treatment, increased the risk of leukemic transformation [24], the Polycythemia Vera Study Group (PVSG) recommended hydroxycarbamide as the chemotherapeutic agent of choice, but without any randomized controlled clinical trials to substantiate this recommendation [25]. Indeed, as discussed later, the recommendation was based on an inadequate duration of observation with respect to the drug's leukemic potential. To date, despite a lack of evidence-based data, hydroxycarbamide continues to be the most widely used drug for PV, high-risk ET and PMF for lack of better alternatives.

In general, it is acknowledged that hydroxycarbamide is effective in reducing the leukocyte and platelet counts in PV patients, as well as the platelet count in ET patients and JAK2 V617F-positive ET patients [18,26,27]. However, given the red blood cell lifespan, suppression of erythropoiesis requires prolonged administration and, thus, hydroxycarbamide is not a substitute for phlebotomy, the effect of which in relieving hyperviscosity is immediate. Hydroxycarbamide can also alleviate pruritus; its effectiveness in reducing spleen size is variable. However, no controlled study to date has demonstrated that hydroxycarbamide prolongs survival in any of the MPDs or that there is a relationship between the platelet count and thrombosis [28,29], although there is a correlation between the magnitude of the platelet count and bleeding [30].

In the few randomized controlled trials that have been performed, hydroxycarbamide did not prevent the development of myelofibrosis in PV at a rate greater than pipobroman [31], and in ET it was effective in preventing transient ischemic attacks but was not superior to aspirin or anagrelide in preventing arterial thrombosis [17,26]. In fact, hydroxycarbamide was inferior to anagrelide in preventing venous thrombosis, presumably because anagrelide is a phosphodiesterase III inhibitor [18,32]. Given the controversy over whether leukocytes



**Figure 3. Hydroxycarbamide-induced inhibition of ribonucleotide diphosphate reductase in proliferating cells to inhibit *de novo* DNA synthesis.**

are central to the development of thrombotic events in PV and ET [33,34], prospective controlled trials examining the effects of leukocyte suppression are clearly indicated, but the routine use of hydroxycarbamide in the MPD is not warranted in the absence of specific indications such as transient ischemic attacks unresponsive to aspirin, cardiovascular risk factors, the need for rapid control of leukocyte or platelet counts because of leukostasis or bleeding, intractable pruritus or intolerance to other agents.

This is particularly true in PV, as pegylated IFN- $\alpha$ , an agent with no DNA-damaging potential, was demonstrated to induce both hematologic remissions and molecular remissions with

### Box 1. Main features of the chronic myeloproliferative disorders polycythemia vera, essential thrombocythemia and primary myelofibrosis.

- Involvement of a multipotent hematopoietic progenitor cell
- Dominance of the abnormal clone over normal clones
- Abnormalities of chromosomes 1, 8, 9, 13 and 20
- High frequency of mitotic recombination, particularly involving chromosome 9
- Familial clustering
- Marrow hypercellularity and megakaryocyte dysplasia
- Growth factor-independent (endogenous) colony formation
- Altered production of one or more of the formed elements of the blood
- Thrombosis and hemorrhage
- Myelofibrosis
- Extramedullary hematopoiesis
- Transformation, but at low and differing frequencies
- Expression of JAK2 V617F and impaired expression or mutation of *Mpl*, but not in all patients
- JAK2 mutations are associated with a specific germline JAK2 gene haplotype

**Table 1. Adverse events associated with hydroxycarbamide therapy for myeloproliferative disorders.**

Adverse event	Frequency of MPD (%)	Ref.
Clinical myelosuppression	6	[18]
Bleeding	10	[18]
<i>Nervous system disorders</i>		
Headache	2	[18]
Dizziness	NA	
Neuropathy (all grades)	NA	
Overall cutaneous disorders	11–89	[18,54,94]
<i>Gastrointestinal disorders</i>		
Nausea/vomiting	3–8	[25,43]
Gastric pain/diarrhea	5	
<i>General disorders</i>		
Fatigue	2–3	[43]
Fever	NA	
Elevated hepatic enzymes	NA	

MPD: Myeloproliferative disorder; NA: Not available.

respect to JAK2 V617F expression in a small Phase II study [35]. Furthermore, these effects were sustained for up to 18 months after IFN- $\alpha$  discontinuation [35,36]. Recently, in a small number of PV and ET patients, hydroxycarbamide was observed to reduce the neutrophil JAK2 V617F allele burden by 20–40% from baseline after 4 months of treatment, after which there was no further reduction; not surprisingly, the response was greatest in those patients with very low allele burdens [37,38], which is not usually the situation in PV [39]. Another study, however, did not demonstrate a significant reduction in the JAK2 V617F allele burden during treatment with hydroxycarbamide [40]. The finding of a decline in the JAK2 V617F allele burden in some patients is not surprising given that hydroxycarbamide reversibly suppresses cell proliferation. However, this effect would not be durable in the absence of the drug, which is not the case in patients being treated long term with pegylated IFN- $\alpha$  [35]. More importantly, whether hydroxycarbamide has any effect at the level of the involved hematopoietic stem cell, which is usually quiescent, is

### Box 2. Definition of resistance/intolerance to hydroxyurea in essential thrombocytosis patients.

- Platelet count <600,000/ml after 3 months of at least 2 g/day of HU (2.5 g/day in patients with a bodyweight >80 kg)
- Platelet count <400,000/ml and WBCs <2500/ml at any dose of HU
- Platelet count <400,000/ml and Hgb <10 g/dl at any dose of HU
- Presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of HU

Hgb: Hemoglobin; HU: Hydroxyurea; WBC: White blood cell.  
Data taken from [45].

unknown. Hydroxycarbamide is not indicated in low-risk ET patients as their lifespan appears to be normal [41]. In fact, it has not been demonstrated that any form of therapy influences the complication rate in these patients [42].

### Tolerability

Hydroxycarbamide toxicity is largely dose related. The nature and frequency of adverse effects in the MPD are shown in TABLE 1. At low doses, hydroxycarbamide generally has little toxicity and is well tolerated [43]. However, when higher doses are used, some patients are unable to tolerate hydroxycarbamide and withdraw from treatment. Rates of patient withdrawal in clinical studies of the MPD are 8–20% [18,25,43,44]. Recently, guidelines have been published for identifying clinical resistance or intolerance to hydroxycarbamide in ET (Box 2) [45].

### General side effects

Several case reports document high fever as a side effect of hydroxycarbamide. Fever developed within hours to weeks of exposure [46], and in some cases was associated with the development of a maculopapular rash and abnormal liver function tests [47]. Hydroxycarbamide-related fever requires drug withdrawal [45]. In a recent case report, a patient presented with shaking chills, fever, fatigue, dizziness and elevated liver enzymes, all of which resolved upon cessation of the drug [47].

### Myelosuppression

Myelosuppression, especially involving granulopoiesis, is the most common side effect of hydroxycarbamide, and may require dose adjustment or discontinuation of therapy [8,48]. Myelosuppression can be more generalized with thrombocytopenia and anemia [48,49]. Thrombocytopenia can be severe (<50  $\times 10^9/l$ ), especially in elderly patients. Unwanted myelosuppression is usually transient and reversible upon drug discontinuation [43]. Hydroxycarbamide therapy can also cause macrocytosis and granulocyte hypersegmentation, which are unrelated to vitamin B12 or folic acid status [48]. In MPD, periodic blood count cycling can occur [50]. Hydroxycarbamide can also induce platelet count cycling with a 28-day periodicity in PV [51]; however, keeping the dose constant appears to dampen the cyclic oscillations [52].

### Cutaneous complications

Cutaneous side effects are very common with long-term hydroxycarbamide therapy [53,54] and include alopecia, xerosis, scaling, and atrophy of the skin and subcutaneous tissues, skin and nail hyperpigmentation, blue lunula, oral and malleolar ulcerations, and solar hypersensitivity (FIGURE 4A) [55,56]. A hydroxycarbamide dermatopathy has also been described in which a poikilodermatous eruption with atrophy, erythema and scaling developed over the dorsal aspects of the fingers and hands (FIGURE 4B) [56].

**Table 2. Hydroxycarbamide-associated acute leukemia in essential thrombocythemia according to median duration of follow-up and del17p status.**

Study (year)	Median follow-up (years)	Study design	Study size (n treated with HC)	Cases of acute leukemia/MDS (% no HC/HC)	Comment	Ref.
Passamonti <i>et al.</i> (2003)	5.6	Observational	605 (147)	0; 5 (3.4)	No cytogenetics	[98]
Palandri <i>et al.</i> (2009)	5.5	Observational	386 (136)	0; 5 (3.7)	No cytogenetics	[29]
Abdulkarim <i>et al.</i> (2009)	15	Observational	374	1 (4.8) <sup>†</sup> ; 17 (81)	In total, 32 out of 56 transformed patients were on HC alone	[97]
Radaelli <i>et al.</i> (2008)	8.6	Observational	331 (116)	1 (0.7); 3 (2.6)	del17p in the untreated patient	[99]
Gangat <i>et al.</i> (2007)	7.0	Observational	605 (165)	5 (2.0); 7 (2.4)	del17p in 4/7 in HC arm	[79]
Sterkers <i>et al.</i> (1998)	8.2	Observational	357 (201)	0; 7 (3.5)	del17p in 3/7 in HC arm	[68]
Bernasconi <i>et al.</i> (2002)	8.7	Observational	155 (23)	0; 4 (17.3)	del17p in 3/4 in HC arm	[66]
Kiladjian <i>et al.</i> (2006)	11.4	Observational	108 (108)	10 (9.3)	No cytogenetics	[78]

<sup>†</sup>One out of 21 untreated patients as compared with 17 out of 21 for hydroxycarbamide. HC: Hydroxycarbamide; MDS: Myelodysplasia.

Moreover, and most importantly, patients on long-term hydroxycarbamide therapy are at increased risk of developing both squamous cell and basal cell carcinomas, typically in sun-exposed areas (FIGURE 4C) but also the oral mucosa [57]. All patients taking the drug need to be aware of solar hypersensitivity and how to avoid it.

Painful cutaneous ulcers are one of the most common and troublesome side effects of hydroxycarbamide therapy (FIGURE 4D) [54]. They typically occur in the malleolar region, often after 5 or more years of treatment, but can also occur at the sites of trauma, venous insufficiency [58] or surgery [31]. Less severe cutaneous changes may occur earlier in a course of treatment, but are not routinely detected without careful examination. The drug must be withheld to allow the cutaneous lesions to heal, which may occur slowly and occasionally may require skin grafting [48]. In a comparative study of hydroxycarbamide and pipobroman, 292 patients with PV aged under 65 years were followed for more than 2 years. A total of 12 out of 133 patients (9.0%) receiving hydroxycarbamide developed leg ulcers, leading to a switch in treatment in ten patients [31]. The development of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of hydroxycarbamide mandates withdrawal of the drug until the lesions heal [45].

#### Gastrointestinal complications

The most common gastrointestinal side effects associated with long-term hydroxycarbamide therapy are oral mucosal ulcerations (4.5%); less common are nausea and vomiting, epigastric pain, and diarrhea [18,31].

#### Respiratory complications

Respiratory side effects including pneumonitis and bronchiolitis obliterans (i.e., inflammation of the bronchioles and surrounding lung tissue) have been reported with hydroxycarbamide therapy; following drug withdrawal respiratory symptoms usually abate [59,60].

#### Treatment-related acute leukemia

##### Mechanisms for hydroxycarbamide-induced mutagenesis

The possibility that hydroxycarbamide is leukemogenic has been a matter of controversy, especially with regard to the MPD. However, the same hydroxycarbamide target involved in DNA



**Figure 4. Examples of cutaneous complications with hydroxycarbamide therapy. (A) Hyperpigmentation of the lunula, (B) erythematous scaly flat papules over dorsal aspect of the hands, (C) cutaneous squamous cell carcinoma and (D) cutaneous ulceration of the toes.**

synthesis – ribonucleotide reductase – is also involved in DNA repair [12]. Thus, hydroxycarbamide has the potential to be mutagenic [61], just like other agents that interfere with DNA repair [62]; indeed, it is widely used experimentally as a dependable clastogen for promoting chromatid breaks [63]. It is also an unequivocal human tumor promoter since it potentiates UV radiation in inducing basal and squamous cell skin carcinomas (FIGURE 4C) and, importantly, it potentiates the leukemogenic effects of alkylating agents and 32P in the MPD whether given before or after them [31,64,65]. In addition, cytogenetic lesions associated with hydroxycarbamide are the same as those seen with other chemotherapeutic agents known to cause acute leukemia, and abnormalities of chromosome 17, such as del17p, which create a state of haploinsufficiency for the tumor suppressor *p53*, appear to be most common with hydroxycarbamide exposure [66–68].

This state of *p53* haploinsufficiency takes on additional importance because, while hydroxycarbamide-induced impairment of DNA synthesis is normally associated with *p53* upregulation and cell cycle arrest [69], in contrast to other mechanisms upregulating *p53* expression the ability of *p53* to transactivate many of the genes involved in DNA repair is blunted by hydroxycarbamide [70]. This is not a significant issue, with the acute mitotic arrest induced by high concentrations of hydroxycarbamide, which usually results in cell death either acutely or by senescence [70,72]. However, at clinically relevant concentrations of hydroxycarbamide, a fraction of the target cell population is able to escape *p53* blockade and cell death and is thus susceptible to the acquisition of mutations [69,71].

Arrested DNA synthesis is also associated with replication fork collapse, which can lead to dsDNA breaks and increased base excision activity [70,72,73]. DNA repair requires both nonhomologous end joining and homologous recombination, functions that *p53* controls to prevent harmful recombination or gene conversion [72,74]. By impairing *p53* transactivation, hydroxycarbamide not only selects for *p53* mutants during the period of proliferative impairment, but also permits uncontrolled nonhomologous end joining and homologous recombination, and otherwise provides a proliferation advantage to transformed cells that would not be competitive with normal hematopoietic progenitor cells. For example, *in vitro*, hydroxycarbamide facilitates BCR-ABL

leukemogenesis by giving cells expressing this fusion tyrosine kinase a growth advantage over normal hematopoietic progenitor cells during S-phase arrest [75].

This is not a trivial effect, particularly with respect to the MPD where hydroxycarbamide is used most frequently, since constitutively active tyrosine kinases such as BCR-ABL and JAK2 V617F promote the generation of reactive oxygen species, dsDNA breaks and unfaithful DNA repair, in effect potentiating the adverse effects of hydroxycarbamide on DNA repair [76]. Importantly, in a recent study JAK2 V617F expression was associated with increased homologous recombination, increased centrosome and ploidy abnormalities, increased sister chromatid exchange, an increased rate of spontaneous mutations in hematopoietic cell lines [77], and a hyper-recombination phenotype in CD34<sup>+</sup> cells from PV and PMF patients similar to that observed in the cell lines, thus creating an internal milieu responsible for promoting hydroxycarbamide mutagenicity.

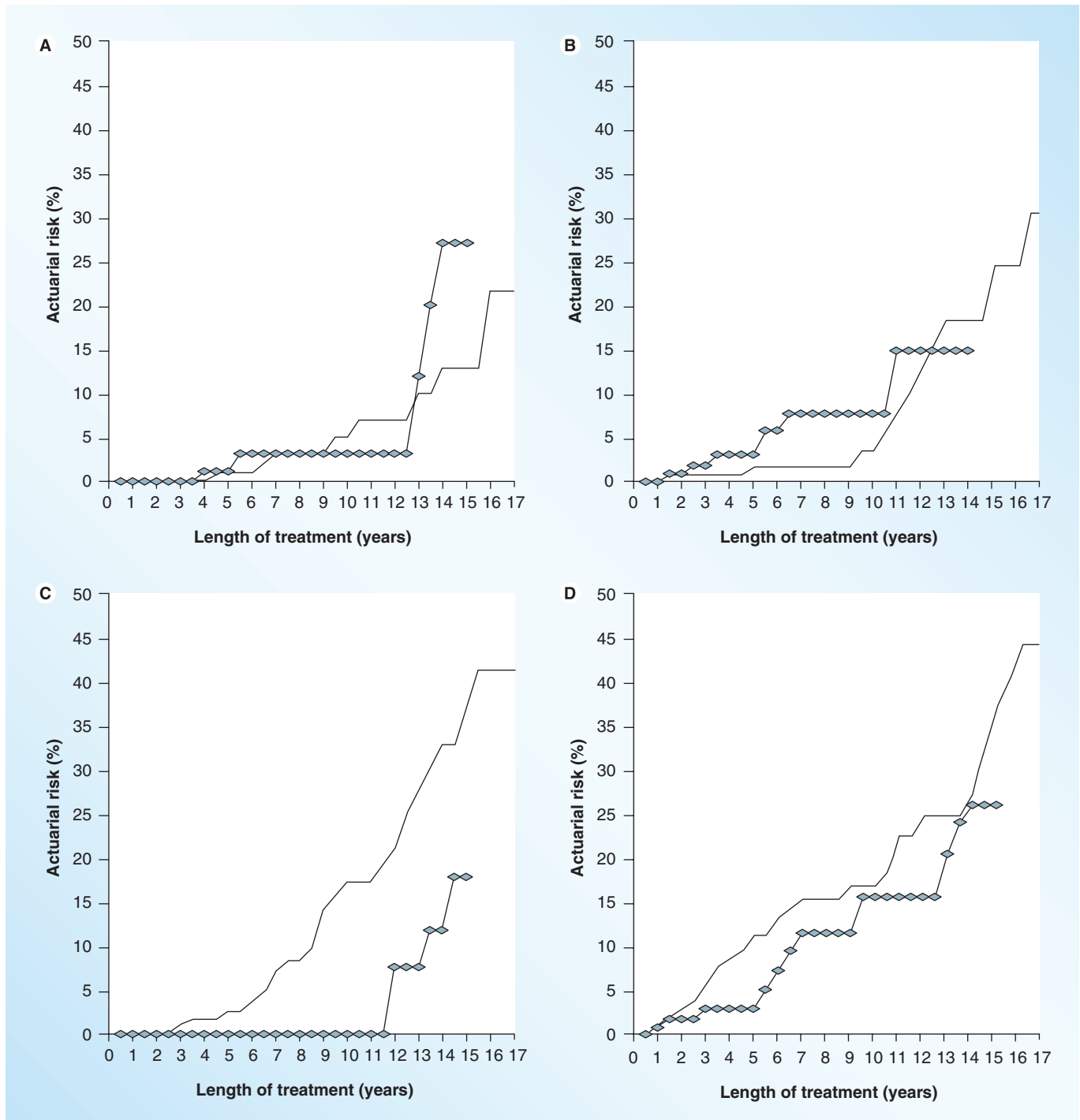
That hydroxycarbamide leukemogenicity in the MPD has been a matter of controversy has been engendered in part by the fact that PV and ET have an intrinsic low but poorly defined spontaneous rate of leukemic transformation, and probably also in part by the very long interval between hydroxycarbamide exposure and leukemic transformation (FIGURE 5, TABLES 2 & 3) [31,78]. For PV, a minimum spontaneous transformation rate of 1.5% has been established [24]. Prospective studies of adequate duration are lacking for ET but leukemic transformation is unlikely to be more frequent [79]. Although a randomized, prospective, controlled clinical trial involving 292 patients established that hydroxycarbamide was leukemogenic in PV with a risk of leukemia of approximately 10% at 13 years [31], this result was not widely accepted despite that fact that subsequent long-term follow-up of these patients documented an increasing incidence of acute leukemia in the hydroxycarbamide-treated study arm without evidence of a plateau, with over 40% of cases occurring after 12 years (14% at 15 years and 24% at 20 years) [78], confirming the earlier observations of the PVSG with alkylating agents and 32P [24].

This controversy has been recently resolved by several studies examining the conundrum of acute leukemic transformation occurring in JAK2 V617F-negative cells in patients with a JAK2 V617F-positive MPD. In one study, there was a statistically significant association of

**Table 3. Hydroxycarbamide-associated acute leukemia in polycythemia vera according to median duration of follow-up.**

Study (year)	Median follow-up (years)	Study design	Study size (n)	Cases of acute leukemia/MDS (%)	Cumulative risk transformation	Ref.
Fruchtman <i>et al.</i> (1997)	8.6	Observational	51	4 (7.8)	NC	[25]
Tatarsky <i>et al.</i> (1997)	7.3	Observational	71	4 (5.6)	NC	[95]
Finazzi <i>et al.</i> (2005)	8.4	Observational	1638	13 (1.2); 10 (1.2)	NC	[96]
Abdulkarim <i>et al.</i> (2009)	15.0	Observational	317	1 (5.5); 5 (27.7)	NC	[97]
Passamonti <i>et al.</i> (2009)	16.0	Observational	70	5 (7.1)	20% at 20 years	[98]
Kiladjian <i>et al.</i> (2006)	16.3	Prospective, randomized	93	5 (16.5)	14% at 15 years (22% at 20 years)	[31,78]

MDS: Myelodysplasia; NC: Not calculated.



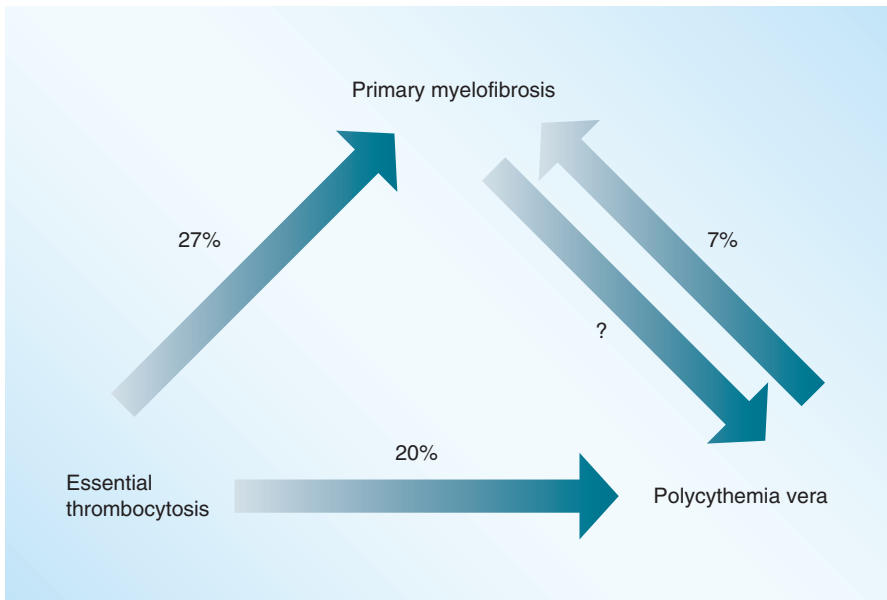
**Figure 5. Actuarial risk of leukemia. (A)** Other cancers, including **(B)** skin carcinoma, **(C)** development of myelofibrosis and **(D)** thromboembolic events (lethal or not) according to the treatment received.

Hydroxycarbamide drawn as a line and pipobroman as blue diamond-shaped symbols.

Redrawn with permission from [31].

del17p acute leukemia in MPD patients receiving hydroxycarbamide alone or in combination with an alkylating agent [80]. In the other study, six out of nine JAK2 V617F-positive PV and ET patients who developed acute leukemic transformation in JAK2 V617F-negative cells had been exposed only to hydroxycarbamide [81]. Importantly, all of these PV and ET patients were in the chronic phase of their

disease, while spontaneous or drug-induced leukemic transformation in JAK2 V617F-positive cells occurred in either PMF patients or PV and ET patients who had transformed a PMF phenotype [81]. Thus, given hydroxycarbamide's known mechanism of action together with the accumulated clinical data, it should no longer be a matter of debate whether the drug is leukemogenic in the MPD [82].



**Figure 6. The inter-relationship between chronic myeloproliferative disorders.**

Schematic diagram illustrating the evolution of phenotype in the chronic myeloproliferative disorders (MPD). For unexplained reasons, both polycythemia vera and primary myelofibrosis can present as isolated thrombocytosis. Therefore, essential thrombocytosis has no phenotype and patients with isolated thrombocytosis should be followed carefully for evolution into another MPD. All pathways converge on polycythemia vera because that disorder is the ultimate expression of JAK2 V617F.

A study by Hanft *et al.* investigated the mutagenic and carcinogenic potential of hydroxycarbamide in MPD patients [83]. Regardless of the duration of hydroxycarbamide therapy (0 months to 18 years), adults did not have increased numbers of acquired DNA mutations compared with controls. These findings, however, should be interpreted cautiously as only committed hematopoietic cells with limited self-renewal activity, if any, were assayed, not pluripotent hematopoietic stem cells, and the duration of hydroxycarbamide exposure was also limited for most of them.

### Fertility

The impact of long-term hydroxycarbamide therapy on fertility is an important consideration for younger patients who might require life-long treatment. In mouse models, hydroxycarbamide produced testicular atrophy, suppressed spermatogenesis, reduced sperm motility, and induced abnormalities in sperm morphology and chromatin structure [84,85]. Experimental evidence suggested that this toxicity was reversible upon treatment withdrawal [86]. Some retrospective data are available on the effect of hydroxycarbamide on sperm function in sickle cell anemia patients taking hydroxycarbamide [87]. Abnormalities were present in all patients before drug exposure and there was exacerbation of these following the institution of therapy, with a marked decrease in sperm volume within 6 months and persistence of this abnormality years after hydroxycarbamide discontinuation. However, although the number of observations was small, fertility did not appear to be affected, nor was there an increase in miscarriages or any birth defects in children fathered by male patients taking hydroxycarbamide.

Hydroxycarbamide is not indicated for women during reproductive years because it crosses the placenta, and experimental evidence suggests that it may be teratogenic [48,88,89]. However, there are no published reports of such effects in humans. Of the 15 identified infants born to women treated with hydroxycarbamide during conception or pregnancy [90–92], no malformations were observed. There was one stillbirth by a woman with eclampsia who had received hydroxycarbamide therapy throughout her pregnancy [92]. Not surprisingly, hydroxycarbamide enters breast milk, and is thus contraindicated in nursing women [93].

### Expert commentary

Hydroxycarbamide is in many ways an ideal chemotherapeutic agent. Water soluble, it is almost completely absorbed in the GI tract and distributed in total-body water, including the cerebrospinal fluid. It enters cells by diffusion, is rapidly metabolized, does not result in the prolonged marrow aplasia characteristic of alkylating agents, has a well-defined mechanism of

action, short effect duration, and can be used to potentiate other chemotherapeutic agents and radiation therapy.

At the same time, based on its mechanism of action and documented effects in the MPD, hydroxycarbamide is genotoxic and should not be employed unless other safer treatments have been tried first. Hydroxycarbamide should not be used in place of phlebotomy in PV or to sanitize the platelet count in PV or ET in the absence of symptoms or evidence of a hypercoagulable state and without trying nongenotoxic options first, since there is no 'safe' platelet count with respect to thrombosis in the MPD. Indeed, the only evidence-based use of hydroxycarbamide in the MPD is to prevent transient ischemic attacks associated with thrombocytosis not responsive to aspirin. While hydroxycarbamide is clinically useful for the temporary suppression of blood counts, relief of pruritus and spleen size reduction when necessary, no study to date has demonstrated improved survival, freedom from major vascular thrombosis or a significant reduction in the JAK2 V617F allele burden despite hematologic remission, while there is ample evidence for its mutagenic potential. Therefore, the lowest dose that produces the desired clinical effect without concern about achieving normal blood counts should be the goal. Hydroxycarbamide use should be avoided, if possible, in conjunction with alkylating agent or 32P therapy because of the very high incidence of acute leukemia that occurs in that setting.

### Five-year view

Despite great progress at the molecular level and the development of useful prognostic scoring systems for primary myelofibrosis, we still lack prognostic scoring systems for PV and ET, and bone marrow



transplantation is the only curative therapy for MPD patients in general. However, this option is not available to all patients because of age considerations, donor availability, comorbidities and a lack of means to determine which PV or ET patients would benefit from early intervention. While JAK2 inhibitors have shown promise in alleviating constitutional symptoms and reducing spleen size in PMF, to date they have not proven effective in reducing the JAK2 V617F allele burden, but PV and ET patients may prove more tractable in this regard since they generally have lower tumor burdens. They are also the MPD patients with the greatest potential longevity and the ones most likely to require therapeutic intervention with genotoxic drugs in the absence of definitive treatment options. The development of acute leukemia in JAK2 V617F-negative cells in patients with a JAK2 V617F-positive MPD supports the contentions that JAK2 V617F is responsible for phenotype but is not the initiating MPD lesion, that the involved stem cells are genetically unstable, and that therapies that eradicate such stem cells will be necessary to

induce molecular remissions in MPD patients. Pegylated interferon has proved effective in this regard and, if the initial clinical trial data are substantiated, this should become the therapy of choice until targeted therapies are developed when treatment beyond phlebotomy, aspirin or anagrelide is needed.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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#### Key issues

- Hydroxycarbamide is a water-soluble chemotherapeutic agent with excellent gastrointestinal absorption that is distributed in total-body water, including the cerebrospinal fluid, enters cells by diffusion, is rapidly metabolized, does not result in the prolonged marrow aplasia, has a well-defined mechanism of action, and can be used to potentiate other chemotherapeutic agents.
- Based on ease of administration, effectiveness and a high level of tolerability, hydroxycarbamide is currently widely used in the management of myeloproliferative disorder (MPD) patients.
- In the MPD, hydroxycarbamide has been proven to be effective for the prevention of transient ischemic attacks associated with thrombocytosis and unresponsive to aspirin therapy.
- Hydroxycarbamide has also been used to control leukocytosis, thrombocytosis and pruritus in MPD patients but, to date, no prospective clinical trials have been conducted to establish clinical criteria for the extent of such blood count control, or to determine whether the drug prolongs survival in MPD patients.
- Hydroxycarbamide has never been demonstrated to prevent major vessel thrombosis or to induce molecular remissions in MPD patients.
- Hydroxycarbamide, by virtue of its ability to create DNA damage, block DNA repair and impede p53 gene activation, creates an environment favorable for the development of gene mutations, particularly those involving chromosome 17.
- Prolonged hydroxycarbamide exposure in MPD has been unequivocally associated with late-onset acute leukemia without evidence of a plateau.
- Hydroxycarbamide potentiates the effects of UV radiation and causes solar hypersensitivity and skin cancers, but many patients are unaware of this.

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