

Busulfan Dosing Literature Review

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Abstract

Introduction: There is debate regarding the use of busulfan every 6 hours (q6 h) compared to every 24 hours (q24 h) in patients undergoing hematopoietic cell transplantation.

Objectives: To review the literature to determine whether there is a significant difference between dosing busulfan q6 h vs. q24 h in adults, and to review dosing strategies to optimize daily dosing.

Methods: A literature search was conducted in PubMed with the terms “busulfan” and “transplant” and “24” in all fields. Results were further refined by using the terms “busulfan” and “transplant” and “pharmacokinetics”. Titles were then reviewed for relevance, and the remaining articles reviewed by abstract. Articles deemed relevant were then read in more thorough detail, and references cited by these articles reviewed to ensure a comprehensive review of the literature. Studies focusing on the pediatric population were not reviewed.

Results: 478 articles were identified, and of these, 372 contained the term “pharmacokinetics”. Based on abstract review, 26 relevant articles were identified. All articles confirmed that there are no differences in the pharmacokinetics of q6 h vs. q24 h dosing, and that safety appears equivalent between the two dosing schemes. One study noted an increase in the occurrence of acute graft-vs.-host disease (GVHD) and possibly increased gastrointestinal (GI) toxicity and stomatitis with q6 h dosing, while another noted a higher incidence of toxicity with q24 h dosing specifically in metastatic renal cell carcinoma patients. All articles concluded that both regimens are equally effective, but that q24 h dosing is more convenient and likely to decrease hospitalization, nursing, and pharmacy requirements.

Conclusions: There is no difference in efficacy or safety between busulfan q6 h and q24 h dosing. Institutions should consider moving to daily dosing of busulfan for improved convenience and decreased costs.

Keywords: Busulfan; Pharmacokinetics; Myelogenous leukemia

Introduction

Busulfan utilization has undergone dramatic progress in hematopoietic cell transplant (HCT) since its initial approval in 1954 [1]. Busulfan is an alkylating agent originally used in chronic myelogenous leukemia (CML), but it has progressively been recognized as a potent myeloablative agent in preparative regimens for hematopoietic cell transplantation (HCT) [2,3]. Busulfan-containing regimens have been widely accepted as a standard of care, and represent the most frequently used myeloablative regimens prior to HCT [4,5].

Busulfan tablets on the market are available only in much smaller doses than those necessary for HCT conditioning [6], as the oral busulfan formulation was originally intended for the CML population [7-9]. This results in a high pill burden for patients on HCT conditioning regimens. Concerns regarding adherence, requiring patients to consume large quantities of pills in a single setting, and the variable systemic bioavailability resulting from a large single oral dose of busulfan led to the development of conditioning protocols that utilize multiple oral doses spread throughout the day, typically at 6-hour intervals [10-13].

Eventually, as high-dose busulfan emerged as an important component of preparative regimens in the early 2000s, intravenous formulations were marketed to overcome the disadvantages of the original oral compound's bioavailability [14]. Alkylating agents are typically dosed at a daily frequency due to cell cycle non-specific activity, and complete bioavailability and elimination of pill burden could theoretically eliminate the necessity of multiple doses in a day [15-25]. Nonetheless, studies comparing intravenous versus oral

administration of busulfan used identical dosing frequencies (again, typically q6 h) in their protocols to avoid confounding variables [26]. Further, it has been found that IV busulfan produces more reliable pharmacokinetic parameters than oral dosing due to its immediate bioavailability and independence from administration with food [27].

There are many disadvantages to high-frequency busulfan dosing. Patients are disturbed more frequently with overnight chemotherapy administrations, possibly impacting recovery and satisfaction. Institutions carry a heavier burden with the resources necessary for admixture, delivery, and nursing administration times with multiple doses per day versus once-daily dosing. Waste can be a significant cost to institutions, since drug waste is produced with each admixture [28]. Due to busulfan's relative short stability, frequent administrations are difficult to batch together [29]. Logically, decreasing the frequency of administration has the potential to improve patient satisfaction, improve convenience, and reduce waste (Figure 1).

As busulfan has been incorporated into more conditioning regimens and additional pharmacokinetic data becomes available,

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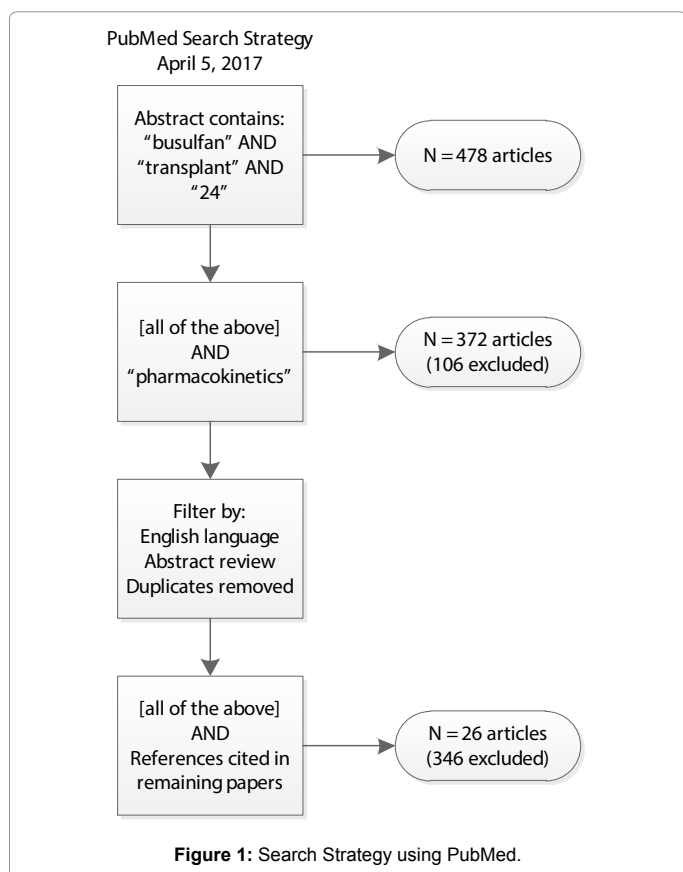
the literature has become more robust with evidence supporting once daily busulfan dosing [30]. To address concerns regarding the safety and efficacy of busulfan IV every six hours (q6 h) compared to every 24 hours (q24 h), we undertook a literature review comparing the two dosing regimens. The objective was to assess the safety, efficacy, and pharmacokinetics to warrant a conversion of regimens that dose busulfan q6 h to an equivalent once-daily intravenous dose.

Methods

Using PubMed, a literature search was conducted with the terms “busulfan” and “transplant” and “24” in all fields. Results were further refined by using the terms “busulfan” and “transplant” and “pharmacokinetics”. Titles were then reviewed for relevance, and the remaining articles reviewed by abstract. Articles deemed relevant were then read thoroughly, and any additional references cited by these articles were reviewed to ensure a comprehensive review of the literature. Figure 1 depicts the search strategy used for this review.

Results

478 articles were identified in the initial search using “busulfan” and “transplant” and “24”. When the terms were changed to include “pharmacokinetics”, 372 articles were identified. Review of abstracts and filter by English language yielded 26 articles relevant to the comparison of IV busulfan q6 h vs. q24 h, or discussed optimal dosing strategies using q24 h dosing. All articles except one concluded that q24 h dosing was feasible, safe, and convenient for both adults and pediatric patients, with clinical equivalence to q6 h dosing. Of the studies reviewed, two found higher rates of toxicity in the q24 h compared to the q6 h regimen [31,32].



One study that found that q24 h dosing had unacceptable toxicity was done in a small sample of seven metastatic renal cell carcinoma patients, six of whom had undergone previous unilateral nephrectomy, and one of whom had renal embolization of a diseased kidney at the time of diagnosis [32]. The authors acknowledged that a combination of kidney deficiency combined with previous exposure to interleukin-2 and combination busulfan with fludarabine likely contributed to the toxicities experienced in their study.

The second study was done in pediatrics, and found that the rate of veno-occlusive disease (VOD) was higher in the q24 h group compared to the q6 h group [31]. However, the same study found that q24 h dosing was a predictor for higher event-free survival and overall survival, and recommended that busulfan IV with therapeutic dose monitoring be used over oral busulfan in children undergoing allogeneic stem cell transplantation, particularly among those at high risk for graft failure or relapse [31].

While an additional study found that the incidence of GVHD tended to be slightly higher in patients receiving busulfan IV q24 h, the authors attributed this to the fact that patients in the q6 h group were younger, and that there was a higher percentage of HLA-matched donors in the q6 h group. This difference was not statistically significant [5].

Overall, most studies focused on the adult population, primarily with AML or CML. Only 3 studies looked at pediatrics, with a collective n=109 patients [31,33,34]. Most studies were done to evaluate the pharmacokinetics of a once-daily dosing regimen. Of these studies, those focusing on pharmacokinetics found that there were either no significant differences in overall pharmacokinetic parameters, or that there was no difference in target area-under-the-curve (AUC) between the two dosing regimens. Although some minor differences were found among the studies for the initial administered dose, most studies evaluated an empiric weight-based dosing regimen of 3.2 mg/kg IV q24 h. Only four studies evaluating busulfan in adults used a dose based on body surface area [35-38]. Despite these differences, pharmacokinetic analysis remains a mandatory component of busulfan administration in order to reach the appropriate target AUC and reduce inter-individual variability [31].

A summary of relevant literature is shown in Table 1.

Discussion

IV busulfan has been a standard myeloablative regimen for HCT for many years. Based on our literature review, dosing busulfan q24 h is comparable in therapeutic efficacy and pharmacokinetic profile to busulfan q6 h.

In in-vitro pharmacodynamic experiments, it appears that the cell’s response to busulfan depends on both concentration and time of exposure [39]. As neither of these factors is exclusive of one another, AUC exposure seems to represent a more relevant pharmacokinetic criterion to correlate its cellular effects. Furthermore, in those same studies, cellular death seemed to not be affected by the dosing schema used to achieve the overall AUC [39].

Anecdotally, we have observed increased nausea and vomiting associated with increased antiemetic utilization, indicating that maximum drug concentration may have a more significant adverse impact on certain organ systems, rather than time of exposure for those systems. Current reports evaluating the toxicity profile between the two dosing regimens focus on major events such as neurotoxicity,

Population	Busulfan Dosing Schedule	Pharmacokinetic Parameters	Safety	Conclusion
Adults with NHL, AML, or CML	1. Bu 1.6 mg/kg IV q12 h × 4 days (n=6) 2. Bu 3.2 mg/kg IV q24 h × 4 days (n=6) 3. All received Cy 60 mg/kg IV q24 h × 2 days	Clearance, half-life, C _{max} and AUC were highly predictive of later dose PK profiles	No CNS or pulmonary toxicity noted	Bu IV can be given safely with reproducible results on a twice-daily divided or single-daily dosing schedule to patients undergoing HSCT.
Adults with AML, CML, MDS, or CLL	Bu 3.2 mg/kg IV q24 h × 4 days+Flu 50 mg/m ² IV q24 h × 4 days (n=70)	The cumulative AUC was comparable to the target range established for Bu PO	No unexpected or unusual toxicity noted	Bu IV is convenient to give, is relatively well tolerated, and gives predictable blood levels
Adults with AML or MDS	Bu 130 mg/m ² IV q24 h × 4 days+Flu 40 mg/m ² IV q24 h × 4 days (n=96)	Clearance in <24 hours with no accumulation and little interdose variation in PK parameters	Well-tolerated, with only one death due to regimen-related complications	Bu IV q24 h yields reproducible and predictable PK with less interdose/interpatient variation vs. Bu PO, and is efficacious with reduced toxicity.
Adults with hematological malignancies	Bu 3.2 mg/kg IV q24 h × 4 days+Flu 30 mg/m ² IV × 4 days (n=10)	C _{ss} target and AUC were comparable to previous studies using fludarabine and oral busulfan	One case of primary graft failure, and one case of Grade 4 hyperbilirubinemia	Targeting single-dose Bu IV yields lower interpatient variability.
Adults with acute leukemias, CML, NHL, MM, MDS, systemic mastocytosis, or myelofibrosis	1. Bu 3.2 mg/kg IV q24 h × 4 days (n=20) 2. Bu 0.8 mg/kg IV q6 h × 4 days (n=11) 3. Bu 1 mg/kg PO q6h × 4 days (n=25) 4. All received Cy 60 mg/kg IV q24 h × 2 days	Bu IV q24 h is clinically equivalent to q6 h dosing, with predictable PK parameters specifically for those with actual body weight ≤ 20% IBW.	Bu IV q24 h had the least amount of GVHD. There were no differences in the incidence of neurologic toxicity, hepatic toxicity, hematologic engraftment, and relapse at 100 days.	Bu IV q24 h is safe, convenient, and consistent for outpatient administration.
Pediatrics with malignant and non-malignant conditions	1. Bu 3.2 mg/kg IV q24 h × 2 days+Flu 30 mg/m ² IV × 5 days (n=30) 2. All received a test dose of Bu 0.8 mg/kg IV × 1	Target AUC and clearance were achieved using information from a test dose of Bu IV.	No patients developed VOD; acute GVHD developed in 11 patients (grades 1-2 in 10, grade 11 in 1).	Bu IV q24 h is feasible, safe, and convenient for administration to children.
Adults with metastatic renal cell carcinoma	Bu 3.2 mg/kg IV q24 h × 2 days+Flu 30 mg/m ² IV × 5 days (n=7)	AUC was higher than predicted from extrapolation of AUC data for the same total dose of Bu IV q6 h.	Patients experienced greater than expected regimen-related toxicity for a reduced-intensity preparative regimen, and the study was stopped.	Bu IV q24 h is associated with unacceptable toxicity compared to Bu IV q6 h, but may be related to fludarabine exposure and having a single kidney.
Pediatrics with malignant and non-malignant conditions	1. Bu 80 mg/m ² q24 h IV+Cy 200 mg/kg IV+Flu 150 mg/m ² IV (n=7) 2. Bu 80 mg/m ² q24 h IV+Cy 120mg/kg IV+Mel 140 mg/m ² IV (n=11)	No accumulation occurred and drug was cleared at 24 hours.	No new or unexpected unusual toxicity.	Bu IV q24 h in children is safe and convenient, and can be dosed based on BSA regardless of age.
Adults with AML, MDS, or CML	1. Bu 130 mg/m ² q24 h IV × 4 days (n=60) 2. Bu 80 mg/kg q6 h IV × 4 days+Cy 60mg/kg IV × 2 days (n=47)	There was no change in estimated clearance, and negligible variability in dose-to-dose PK or interdose accumulation.	There was no increase in any toxicity, particularly neurotoxicity.	Bu IV has highly predictable, linear PK, and, Bu q24 h IV is more convenient.
Adults with ALL or AML in 1 st and 2 nd remission	Bu 3.2 mg/kg q24 h IV × 4 days+Flu 50 mg/m ² IV+TBI 200 cGy × 2 days	PK analysis was not performed.	The regimen was well-tolerated.	Bu IV q24 h+Flu +TBI is well tolerated and gives equivalent final outcomes from match-related and alternate donors.
Adults with AML, ALL, CML, MDS, or other	1. Bu 3.2 mg/kg IV q24 h × 4 days+Cy 60 mg/kg IV × 2 days (n=13) 2. Bu 3.2 mg/kg IV q24 h × 2 days+Flu 3 mg/kg IV × 6 days (n=16) 3. Bu 0.8 mg/kg IV q6 h × 4 days+Cy 60 mg/kg IV × 2 days (n=12) 4. Bu 0.8 mg/kg IV q6 h × 4 days+Flu 3 mg/kg IV × 6 days (n=17)	PK parameters were not statistically significantly different except for C _{max} .	There were no significant differences in acute GVHD and VOD, although incidence of acute GVHD was 31.0% in the Bu IV q6 h group vs. 13.8% in the Bu IV q24 h group (p=0.145). Other toxicities observed within 100 days after transplantation were not significantly different.	PK profiles and posttransplant complications are similar for Bu IV q24 h and Bu IV q6 h with similar number of posttransplant deaths and overall survival.
Pediatrics with malignant and non-malignant conditions	1. Bu 120 mg/m ² IV q24 h × 4 days (n=30) 2. Bu 1 mg/kg PO q6 h × 4 days (n=31) 3. All also received either Cy+Mel, Cy, Flu, or CY+VP16	The mean total AUC was higher than the target, indicating that PK analysis is necessary for interdose adjustment.	Bu IV q24 h was associated with more cases of VOD in patients who also received Cy and Mel.	Bu IV q24 h resulted in higher event-free and overall survival compared to Bu PO.
Review article	1. Bu IV 2. Bu PO	No accumulation or increased exposure occurs with Bu IV q24 h dosing.	Bu IV q24 h is associated with less GI toxicity/stomatitis and acute GVHD compared to q6 h dosing.	Bu IV q24 h in myeloablative doses appear equally effective and perhaps more convenient compared to Bu IV q6 h.
Adults with AML, MDS, CML, lymphoma, MM, or other	1. Bu 3.2 mg/kg IV q24 h × 4 days (n=22) 2. Bu 0.8 mg/kg IV q6 h × 4 days (n=24)	Clearance, volume of distribution, and half-life did not differ between the two groups.	There are no differences in the incidence of VOD or elevated bilirubin between q24 h and q6 h dosing	PK parameters are linear, stable, and predictable, and unaffected by co-administration with Flu.

Adults with AML, ALL, CML, MDS, or other	1. Bu 3.2 mg/kg IV q24 h × 4 days (n=30) 2. Bu 0.8 mg/kg IV q6 h × 4 days (n=30) 3. All also received either Cy, Flu, or Bu only	PK parameters were used to develop a new dosing scheme for Bu IV q24 h.	Not assessed.	Bu dosed at 24.79*ABW ^{0.5} mg IV q24 h reduces interindividual variability in clearance and volume of distribution.
Adults with AML, ALL, CML, NHL, MM, HD, MDS, myelofibrosis, or other	1. Bu 3.2 mg/kg IV q24 h × 4 days+Flu 50 mg/m ² × 5 days (n=335) 2. Different test dose strategies evaluated	Test and treatment dose should be infused at the same rate to accurately predict therapeutic doses.	Not assessed.	A test dose for Bu IV q24 h is accurate as long as it is infused at the same rate as the treatment dose.
Adults with ALL	Bu 3.2 mg/kg IV q24 h × 4 days+Clo 40 mg/m ² IV × 1 day (n=51)	PK-guided Bu IV led to accurate dose delivery within a tight therapeutic window.	Bu IV q24 h in combination with Clo is well-tolerated with no cases of VOD.	Bu IV q24 h+Clo produces excellent disease control in ALL with favorable toxicity profile.
Adults with AML, MDS, CML, CLL, myelofibrosis, or other	1. Bu 3.2 mg/kg IV q24 h × 4 days+Cy 60 mg/kg IV × 2 days (n=42) 2. Bu 3.2 mg/kg IV q24 h × 4 days+Flu 30 mg/m ² IV × 4 days+rATG (n=29) 3. Bu 3.2 mg/kg IV q24 h × 4 days+Flu 50 mg/m ² IV × 5 days+rATG (n=16)	Bu 3.2 mg/kg IV q24 h led to suboptimal C _{SS} , while Bu 4 mg/kg achieved the desired C _{SS} . There is minimal dose-to-dose variability of busulfan clearance.	Not assessed.	TDM should be conducted by sampling over a minimum of 8 hours after the start of infusion.
Adults with CML, CLL, MDS, MM, NHL, HD, myelofibrosis, or other	Bu 3.2 mg/kg IV q24 h × 2 days+Flu 50 mg/m ² IV × 5 days (n=158)	Target AUC was achieved and led to improved outcomes when daily Bu exposure was 3814-4994 μM/min.	Patients achieving target AUC had the lowest rates of acute GVHD.	Bu IV q24 h is effective in achieving targeted AUC and yields similar outcomes to q6 h dosing. Target AUC may differ based on the conditioning protocol and the disease.
Adults with relapsed MM	Bu 3.2 mg/kg IV q24 h × 2 days+Btz 1.3 mg/m ² × 1 day (n=30)	An outpatient test dose of Bu IV led to only 2 of 30 patients requiring dose adjustment based on confirmatory PK.	No abnormal toxicity was noted among patients achieving target AUC.	Targeted dose Bu IV q24 h in combination with bortezomib is effective with acceptable toxicity.
Adults with ALL, AML, CML, NHL, or other	1. Bu 130 mg/m ² IV q24 h × 4 days+Flu 40 mg/m ² IV × 4 days (n=18) 2. Bu 0.8 mg/kg IV q6 h × 4 days+Cy 60 mg/kg IV × 2 days (n=13)	All patients required dose adjustment to achieve target AUC, but using actual body weight led to more accurate dosing.	No patients experienced busulfan-related toxicity.	No differences were noted related to dosing frequency; further study needed to determine optimal weight to achieve target AUC.
Adults with AML, ALL, MDS, Hodgkin's lymphoma, or other	1. Bu 3.2 mg/kg IV q24 h × 4 days+Cy 60 mg/kg IV × 2 days 2. Bu 3.2 mg/kg IV q24 h × 4 days+Flu 30 mg/m ² IV × 6 days 3. Bu 3.2 mg/kg IV q24 h × 4 days+Mel 140 mg/m ² × 1 day	Median AUC was similar to other studies of Bu IV q24 h and estimated daily AUC based on Bu IV q6 h studies.	No patients experienced VOD, and no regimen-related toxicity was significantly associated with AUC.	Bu IV q24 h has a stable PK profile and is more convenient than q6 h dosing.
Adults eligible for HSCT	1. Bu 3.2 mg/kg IV q24 h × 2 days+Flu 30 mg/m ² IV × 5 days (n=19) 2. Bu (23 × AB ^{0.5}) mg IV q24 h (n=18) 3. All also received either Flu+ATG, Cy, or Flu	Using a population PK model with dosage history and demographic data can optimize the busulfan dose required to achieve target AUC.	Not assessed.	Bu IV q24 h dosed using a novel scheme based on actual body weight may result in better PK compared to 3.2 mg/kg dosing.
Adults with NHL or Hodgkins lymphoma	1. Bu 2.8 mg/kg IV q24 h × 4 days+Cy+VP16 16 mg/m ² × 5 days (n=93) 2. Bu 0.8 mg/kg IV q6 h × 3.5 days (n=307)	There is a significant range of AUCs with a standard deviation of 13%.	There was no increase in pulmonary or hepatic toxicity.	Bu IV q24 h is more convenient than Bu IV q6 h with equivalent clinical outcomes.
Practice Guidelines Committee of the American Society of Blood or Marrow Transplantation (ASBMT)	N/A; the document is a compilation of FAQ's regarding personalized busulfan dosing	Bu clearance, volume of distribution, and half-life are similar regardless of whether Bu IV is given q6 h or q24 h.	It has been demonstrated that q24 h dosing is safe.	Bu IV q24 h is clinically equivalent to Bu IV q6 h.
Adults with AML, CML or MDS	1. Bu IV q6 h × 4 days+Cy (n=495) 2. Bu IV q24 h × 4 days+Flu (n=331) 3. Bu IV q24 h+Cy (n=96) 4. Bu IV q6h+Flu (n=91)	There are no differences between Bu IV q24 h and Bu IV q6 h.	Cumulative incidence of VOD, idiopathic pneumonia, and seizures did not differ across groups.	Bu IV q24 h and Bu IV q6 h alone or in combination with Cy or Flu have similar outcomes in the myeloablative setting for treatment of myeloid malignancies.

ALL: Acute Lymphocytic Leukemia; AML: Acute Myelogenous Leukemia; AUC: Area Under the Curve; CLL: Chronic Lymphocytic Leukemia; CML: Chronic Myelogenous Leukemia; GVHD: Graft-Versus-Host Disease; HD: Hodgkin's Disease; HSCT: Hematopoietic Stem Cell Transplant; MDS: Myelodysplastic Syndrome; MM: Multiple Myeloma; NHL: Non-Hodgkin's Lymphoma; VOD: Veno-Occlusive Disease; TDM: Therapeutic Dose Monitoring.

*Dosing unspecified

Table 1: A summary of relevant literature.

hepatotoxicity, engraftment, and overall survival [37]. However, there are still significant and common adverse effects that may affect the patient's quality of life that may not be reflected in those categories. These are important to look into further as we continue to adopt this approach. Although existing literature describes major toxicities associated with busulfan (i.e., seizures and sinusoidal obstructive

syndrome (SOS) that are equivalent when pharmacokinetic monitoring assumes equal AUC concentrations, a larger study is warranted to verify these claims [5,40,41].

Busulfan is available in 60 mg vials, and is typically dosed at a starting dose of 0.8 mg/kg q6 h, or 3.2 mg/kg q24 h (with subsequent

pharmacokinetic adjustment) for a total of four days as part of a myeloablative regimen prior to HCT [4]. With q6 h dosing, a typical 75 kg patient would receive 67.5 mg per dose, therefore requiring 2 vials per dose and 8 vials per day, for a total of 32 vials per patient per treatment course. Using less frequent q24 h dosing, the same patient would receive a typical dose of 270 mg per day, requiring 5 vials per day for a total of 20 vials per patient per treatment course. Reducing the dosing frequency to daily administration therefore results in a 63% reduction in the necessary busulfan purchasing in this typical situation (from 1,920 mg to 1,200 mg), translating into significant direct drug cost savings with identical clinical efficacy. Busulfan is a relatively expensive medication; according to the Veterans Affairs Federal Supply Schedule, the intravenous form costs approximately \$935.72 per vial in the US, implying that converting from q6 h to q24 h dosing could save at least \$11,000 per patient in direct drug costs.

Not only does the reduced dosing frequency yield direct drug cost savings, but it also decreases pharmacy resources required to prepare the IV admixture from four times daily, to just once per day. In particular, busulfan's stability is only 12 hours once admixed, so daily administration is more practical for pharmacy [34]. Nursing administration is also simplified with a once-daily regimen. Nursing and pharmacist workloads have been shown to impact medication safety, provider burnout, and job satisfaction [42,43]. Switching from q6 h to q24 h busulfan administration can thus have a positive impact on both patient safety and provider satisfaction. Finally, as patient satisfaction is increasingly utilized as an important metric of care quality, it seems reasonable to assume (although it remains to be proven) that patient satisfaction will increase with fewer interruptions and less frequent medication administration.

In an informal poll of 24 institutions that perform HCT, we found that 20 (83.3%) were already utilizing q24 h dosing. Although this was an informal poll with a small sample size, the results imply that institutions are moving towards this practice, but also that q6 h dosing remains in use at a significant minority of large transplant centers.

Conclusion

Based on the available literature, busulfan IV q24 h is comparable to q6 h dosing in both safety and efficacy. Future research should focus on busulfan dosing in pediatric patients, given that the current evidence for once-daily busulfan is not as compelling as that for adults. Another important area for research should focus on identifying the significant differential toxicities associated with q6 h vs. q24 h dosing. Institutions utilizing busulfan q6 h dosing should consider switching their practice to q24 h to reduce costs and administration resources, and improve patient quality of life.

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