Review Article

Clinical Relevance of Therapeutic Drug Monitoring of Busulfan-Based Regimens in Adult Hematopoietic Stem Cell Transplant Patients

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Abstract

Hematopoietic stem cell transplant (HSCT), also known as bone marrow transplantation, is a therapeutic procedure that revolutionizes the treatment landscape for various debilitating conditions, including hematological malignancies and genetic disorders. Busulfan, an alkylating agent, plays a pivotal role in this regimen by eradicating malignant tumor cells and replacing unhealthy cells with healthy ones. In recent years, therapeutic drug monitoring (TDM) has emerged as a valuable tool for optimizing the dosing strategies of busulfan-based regimens in adult HSCT patients. This narrative review aims to comprehensively assess the clinical relevance and significance of TDM explicitly about busulfan-based regimens in adult HSCT patients. This review explores and analyzes existing literature, focusing on the efficacy, safety, and practical implications of utilizing TDM to optimize busulfan dosing strategies in this patient population. A review of English written literature on PubMed, Google Scholar, and Cochrane Library was performed on the terms "busulfan and pharmacokinetics" and "transplant and conditioning". The evidence is presented first on factors influencing Busulfan clearance and volume distribution. Then, the need to implement TDM of busulfan-based regimens in adult patients is discussed. A large-scale trial is required to demonstrate the benefit of anticipating and avoiding Adverse Drug Reactions and sufficient dosage to reach desired objectives. Future research on TDM of busulfan-based regimens in adult HSCT patients must address several critical issues.

Keywords: Busulfan, Pharmacokinetics, Hematopoietic, Transplant, Conditioning, Monitoring

Introduction

Hematopoietic stem cell transplant (HSCT), commonly known as bone marrow transplantation, provides healthy hematopoietic stem cells to patients with depleted or defective bone marrow and enhances the function of the bone marrow. HSCT can destroy malignant tumor cells, depending on the condition being treated. Additionally, in conditions such as hemoglobin disorders, immunological deficiency syndromes, and other illnesses, HSCT can produce healthy cells to replace unhealthy ones [1].

In both children and adults, HSCT is the recognized treatment of choice for several cancerous and non-cancerous disorders. HSCT was first created as a cancer patient's rescue therapy following extensive radiation and chemotherapy treatments and correction of severe hematopoietic system deficits, then used as adoptive immunological therapy for autoimmune diseases and cancers [2]. HSCT refers to the transfer of hematopoietic stem cells that are either autologous (from the patient) or allogeneic (from a donor) with the intention of partially or entirely replacing the hematopoietic system [3].

By repairing congenital or acquired defects in blood cell production and immune function (allogeneic HSCT), restoring hematopoiesis following high-dose cytotoxic therapy for malignancy, and providing anticancer immunotherapy (allogeneic HSCT), also known as graft versus tumor, HSCT may be an effective treatment for a wide range of diseases [4]. The resource availability as Labs with less funding would not have easy access to specialist

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TDM assays or result in interpretation knowledge. Variations in monitoring practices may result from this. Variability in TDM procedures may result from the inconsistent application of protocols, guidelines, or the absence of established standards [5]. Their knowledge and expertise with TDM can significantly impact a doctor's practice. Effective TDM requires comfort with reading drug levels and using them to inform therapeutic decisions. Sixth, TDM accessibility and accuracy could be enhanced by new technologies such as point-of-care testing instruments. However, their adoption differs depending on the context [5].

Therapeutic Drug Monitoring (TDM] is a clinical procedure that optimizes each patient's dosing schedule by measuring particular medications at predetermined intervals to keep a steady concentration in the patient's circulation. Drugs with restricted therapeutic ranges, significant pharmacokinetic variability, hard-to-monitor target concentrations, and documented side effects are the primary candidates for TDM [6]. The methodology presupposes a measurable correlation between dosage and drug concentration in the blood or plasma and between concentration and therapeutic outcomes.

TDM starts with the prescription of the medication and includes figuring up the first dosage schedule according to the patient's age, weight, organ function, and concurrent pharmacological therapy. The sampling period, dosage history, patient reaction, and intended medication targets are considered when interpreting concentration values [6]. TDM is essential to the best possible medication therapy for adult recipients of HSCT. In HSCT, diseased cells are removed with high-dose chemotherapy and occasionally radiation therapy. The hematopoietic system is then regenerated by infusing stem cells. TDM aids in minimizing toxicity, ensuring therapeutic efficacy, and modifying medication dosages in these patients [7].

TDM is used for several medications, including chemotherapeutic agents, antimicrobials (such as antibiotics and antifungals), and immunosuppressants (such as tacrolimus and cyclosporine). Because of the changed pharmacokinetics following transplantation, it helps to maintain appropriate medication levels [8]. For instance, tacrolimus and cyclosporine are frequently administered to stop graft-versus-host disease (GVHD). TDM ensures these medications prevent toxicity while having the intended immunosuppressive effect [9]. As HSCT patients are more prone to infections because of their immunosuppression, TDM aids in maintaining therapeutic concentrations and preventing resistance to antibiotics (e.g., vancomycin, gentamicin) and antifungals (e.g., voriconazole, posaconazole) [10]. To avoid relapse or control residual disease, TDM is relevant for medications used in conditioning regimens or post-transplant chemotherapy. Methotrexate, cyclophosphamide, busulfan, and so on are some examples [11].

In HSCT patients, pharmacokinetics changes due to fluctuating drug distribution, metabolism, excretion, and absorption after transplant. This necessitates close observation due to mucositis, renal or hepatic impairment, drug interactions, and individual variability. TDM enables tailored treatment, guaranteeing the appropriate dosage for each patient, reducing side effects, and maximizing therapeutic results. TDM is essential to the management of medication therapy in adult HSCT patients. It improves outcomes by minimizing side effects and balancing therapeutic efficacy [12]. For HSCT patients, institutions frequently create particular TDM protocols that include sample schedules, target drug concentrations, and dose modifications depending on the patient's characteristics and these levels.

TDM practices vary significantly due to several factors within the same healthcare centers, countries, and institutions. First, the requirements for TDM vary throughout medication classes. Certain drugs have limited therapeutic indices, meaning careful monitoring is necessary to guarantee effectiveness and reduce side effects. Others may need to be monitored in particular circumstances and have broader therapeutic ranges [13]. Second, variations in age, genetics, and comorbidities might affect how medicine is metabolized and responded to, requiring modifications to treatment management plans [14, 15]. Several challenges may prevent TDM from being implemented successfully. TDM is resource-intensive and frequently requires costly assays and specialist knowledge. This may restrict patients' access to TDM in environments with limited resources.

Healthcare practitioners may operate inconsistently and in perplexity if there are no clear and uniform rules for TDM. Data interpretation and application can be challenging. Integrating TDM with electronic health records may aid clinical decision-making and increase accessibility; however, technological and data protection concerns frequently hamper this integration. Effective TDM necessitates the involvement of medical professionals, including physicians, pharmacists, and laboratory personnel. TDM initiatives can fail because of a lack of communication and coordination. Patients must understand the value of TDM and how to participate in the procedure correctly. This necessitates constant education and assistance from healthcare providers [16].

Developing evidence-based guidelines, investing in healthcare workers' training, incorporating technological developments, fostering teamwork, increasing patient participation, and conducting research are all options for improving TDM practices and overcoming difficulties. These measures guarantee that practices are consistent across contexts, improve patient care, and use drugs safely. More research is needed to assess the efficacy of various TDM tactics and discover cost-effective alternatives [17].

Busulfan is an alkylating, cell-cycle phase-non-specific chemotherapeutic agent metabolized by hepatic enzymes such as Glutathione-S-Transferase and cytochrome P450 enzymes. Busulfan acts by alkylating DNA, thus interfering with DNA replication and RNA transcription, ultimately disrupting nucleic acid function. It produces guanine-adenine intrastrand crosslinks in DNA and is hydrolyzed, releasing methanesulfonate groups and producing carbonium ions that alkylate DNA [18]. Busulfan is combined with other chemotherapy or radiation as a conditioning regimen before allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous myeloid, myelocytic, and granulocytic leukemia. It is also used as a component of pretransplant conditioning regimens in patients undergoing bone marrow transplantation for acute and chronic myeloid leukemia and non-malignant diseases [19, 20]. Busulfan can be taken orally or intravenously

Conditioning regimens are essential preparatory treatments used before HSCT. Their key objectives are to eliminate malignant cells, lower the likelihood of illness return following transplantation, suppress the immune system to prevent the transplanted stem cells from being rejected, and allow them to engraft in the recipient's bone marrow. This will create space for transplanted stem cells to settle and begin making new blood cells [21]. Conditioning regimens can be divided into Myeloablative Conditioning (MAC) and reduced-intensity Conditioning (RIC).

MACs are high-intensity conditioning regimens that use large doses of chemotherapy and total body irradiation (TBI) to eradicate the patient's bone marrow used in aggressive conditions where the current bone marrow must be removed entirely [22]. Compared to MAC, RIC is a less intensive regimen with fewer chemotherapy sessions and TBI dosages. They suppress the patient's immune system enough to allow donor cells to engraft without removing their bone marrow. They are used for elderly or fragile patients who may be unable to withstand the toxicity of MAC [23].

The decision between Myeloablative Conditioning (MAC) and Reduced-Intensity Conditioning (RIC) in the context of medical treatments is influenced by various factors [24]. These factors encompass a range of considerations, such as the patient's overall health status, age, comorbidities, and the specific disease or condition being targeted. The choice between MAC and RIC also considers the balance between achieving a sufficiently intense treatment to eradicate the disease and minimizing the potential for severe side effects or complications. Additionally, the availability of suitable donor options, such as matched unrelated donors or haploidentical donors, plays a pivotal role in guiding this decision-making process [25, 26].

Younger and healthier individuals usually tolerate patient age and fitness level as MAC, but RIC may be preferable for older or fragile patients. Disease type and risk of relapse as MAC may be required for aggressive diseases with a high probability of relapse, but RIC may be sufficient for less aggressive diseases. Donor-type MAC is usually recommended for allogeneic HSCT, whereas RIC can be used for autologous HSCT [4, 24].

The following **Table 1** summarizes the main distinctions between MAC and RIC [27]:

Table 1. Distinctions between MAC and RIC

Feature	Myeloablative Conditioning (MAC)	Reduced-intensity Conditioning (RIC)
Intensity	High	Low
Goal	Complete eradication of bone marrow	Suppression of the immune system and partial eradication of bone marrow
Regimen	High doses of chemotherapy and/or TBI	Lower doses of chemotherapy and/or TBI
Toxicity	Higher	Lower
Patient suitability	Younger and healthier patients	Older or frail patients
Disease types	Aggressive diseases with a high risk of relapse	Less aggressive diseases
HSCT type	Allogeneic HSCT	Autologous HSCT

Research Gap

Busulfan also has a narrow therapeutic index, which explains the difficulty in achieving desired serum concentrations, both below the threshold of toxicity and above the threshold of clinical benefit. Due to its narrow therapeutic index, busulfan administration necessitates continuous monitoring. Most of the available data on Busulfan is in the pediatric population. Adult patients may present or proceed differently than pediatric patients for many reasons, including past medical histories, comorbidities, and disease types.

Aim

This narrative review aims to comprehensively assess the clinical relevance and significance of TDM of busulfan-based regimens in adult HSCT patients. This review explores and analyzes existing literature, focusing on the efficacy, safety, and practical implications of utilizing TDM

to optimize busulfan dosing strategies in this patient population.

Materials and Methods

A review of English written literature on PubMed, Google Scholar, and Cochrane Library was performed on the terms "busulfan and pharmacokinetics" and "transplant and conditioning." The evidence will be presented first on factors influencing Busulfan clearance and volume distribution. Then, the need to implement TDM of busulfan-based regimens in adult patients is discussed. Finally, limitations in the current literature and challenges in recommendations are presented.

Results and Discussion

Factors Influencing Busulfan Clearance and Volume Distribution

This section will discuss the Influence of age, weight, and enzyme expression on the metabolism of Busulfan.

Due to developmental changes in the enzyme systems responsible for drug metabolism, the metabolism of medicines such as Busulfan in pediatric patients, particularly newborns and young children, might differ dramatically from that of adults. As a child develops, enzymes involved in medication metabolism (cytochrome P450 enzymes) may mature, affecting the clearance of pharmaceuticals such as Busulfan [28, 29]. Busulfan dosing frequently incorporates weight-based calculations, particularly in young patients, to provide optimal therapeutic levels while minimizing toxicity [30, 31].

The volume distribution of medications in the body can be influenced by weight. A more significant volume of distribution for Busulfan may arise from a higher body weight [32]. Busulfan is primarily metabolized in the liver by CYP enzymes, specifically CYP2C9 and CYP3A4. Variations can influence individual drug metabolism rates in the expression and activity of these enzymes caused by genetic variances. Polymorphisms in these enzymes can cause variable rates of drug metabolism, influencing clearance and total drug levels in the body [33].

Table 2 presents data on various transplant trials/studies, detailing age groups, indications, transplant types (Allogeneic vs Autologous), target AUC defined per the study, doses administered, results, and key findings. This comprehensive overview aids in understanding the diverse outcomes in the field of transplantation research.

Table 2. Outcomes of Transplant Trials Across Age Groups and Indications"

Trial/Study Type	Age group	Sample Size	Indication	Type of transplant (Allogeneic vs autologous)	Target AUC Defined per study	Doses administered	Results	Findings
(C. Seydoux *et al.*) [34]	Adults	300 patients	Acute myeloid leukemia (AML), Myelodysplastic syndrome (MDS), Myeloproliferative neoplasia (MPN), chronic myeloid leukemia (CML)	Allogeneic	Bu-1 - 4680–5848 µmol/l*min Bu-4 - 900–1350µmol/l*min	Bu-1 - 3.2 mg/kg over three h Bu-4 - 4 × 0.8 mg/ kg over 2 h	Bu-1 - 4217 µmol/l*min Bu-4 - 1008 µmol/l*min	Pharmacokinetics did differ significantly according to the number of doses given per day. Ninety (36%) patients were in low AUC,127 (50%) were in range, and 36 (14%) were in high AUC with Bu-4. Comparatively, more than half of the patients (66%) were in low AUC, and only 11% were in high AUC with Bu-1 ($p<0.01$).
(Andersson *et al.*, 2000) [35]	Ages16-35 years	15 patients	Hematologic malignancies	Allogeneic	1100 to 1200 µmol/L	0.52mg/kg (iv) 1.0mg/kg (oral)	1189 µmol/L per min (iv) 1135 µmol/L per min (oral)	Bu administration via the IV route will assure complete bioavailability and reliable systemic drug exposure with more predictable blood levels and, therefore, possibly lower the risks for severe/life-threatening toxicity, graft rejection, and recurrent leukemia.

(Madden *et al*., 2007) [36]	Adults	60 Patients Sample: not mentioned			Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)	Allogeneic	NA	130 mg/m2 once daily or 0.8 mg/kg (approximately 32 mg/m2) every 6 hours	4871 microM x minute (once daily) 1,292 microM x minute 6 hourly)	Intravenous Busulfan has highly predictable, linear pharmacokinetics from 32 mg/m2 (0.8 mg/kg) every 6 hours to 130 mg/m2 once-daily intravenous busulfan dosing is convenient.
(Chen *et al*., 2021) [37]	Adults and children	Age 21 1.5 55 50 5 16 7	Gender F M M F M M M	Disease AML LNS AML AML ALD AML NB	Hematopoietic cell transplantation	Allogeneic	10 to 10,000 ng/mL	Young adults, target busulfan AUC of 90 mg × h/L	Patient A 0.71 ± 6.17% Patient B 3.49 ± 3.88% Patient C 7.77 ± 3.14%	Busulfan concentrations at the four-time points in three patients were between 11.53 and 6.73%, and the average differences (mean ± standard deviation) were 0.71 ± 6.17% in patient A, 3.49 ± 3.88% in patient B, and 7.77 ± 3.14% in patient C.
(Russell & Kangarloo, 2008) [38]	Adults	Not specific			Hematopoietic stem cell transplantation	Allogeneic	900-1,500M. min	Oral: 1.2mg/kg IV: 0.8mg/kg	900-1,500M. min (80%)	Studies of test dosing of IV Bu show that this strategy is more accurate when test and treatment doses are infused at the same rate. Finally, targeting exposures to the upper end of the therapeutic range may provide a safe approach to exploiting dose intensity to treat some malignancies.

AUC: Area under the curve, Bu-1: Busulfan once daily, Bu-4: Busulfan 4 times daily, VOD: Veno-Occlusive disease, TDM: therapeutic drug monitoring, NA: Not available

The Need for TDM of Busulfan-Based Regimens in Adult Patients

TDM is an essential technique in adult HSCT, allowing for precise dose, tailored therapy, and limiting toxicity. Due to the inter-patient variability in the metabolism of Busulfan, individualized dosage changes can be made to ensure target drug concentrations [39, 40]. TDM also helps to prevent overdose and reduces the risk of side effects by keeping therapeutic levels within a reasonable range. Maintaining therapeutic levels is critical for attaining desired HSCT results like engraftment and disease management [41, 42]. TDM aids in the maintenance of medication levels linked with better Graft-Versus-Host Disease (GVHD) control, potentially increasing patient recovery. Numerous studies have shown that TDM improves results, reduces toxicity, and increases patient survival rates in Busulfan-based regimens. National and international guidelines are increasingly recommending TDM for Busulfan to ensure therapeutic efficacy and avoid side effects in HSCT [34, 43]. Continuous monitoring and modifications are also required, with real-time monitoring allowing clinicians to make daily dose adjustments. Adaptive therapy can be modified in response to changing patient situations, potentially improving treatment outcomes [35, 36].

TDM-guided busulfan dosing enhances engraftment rates in HSCT patients while lowering toxicity and the risk of adverse events such as hepatotoxicity and pulmonary toxicity [37, 38]. It also improves overall survival while decreasing disease-free survival in patients with specific disorders [44-46]. TDM-guided therapy can result in shorter hospital stays, lower costs, and more patient satisfaction [45]. It is considered cost-effective because it can shorten hospital stays, prevent treatment failure, and reduce complications. Standardized care across healthcare institutions offers high-quality care while allowing for additional study. TDM also promotes patient empowerment by providing transparent information about drug levels, which may lead to better adherence to treatment regimens [46]. TDM's importance in optimizing HSCT therapy is predicted to grow as technology progresses.

Considerations for Clinical Practice

Because Busulfan metabolism varies, especially in pediatric patients, TDM is frequently used to ensure the drug's concentration remains within the intended therapeutic range. Individualized Dosing strategy may be required to optimize therapeutic effects while avoiding toxicity due to age, weight, and genetic variations.

Understanding how age, weight, and enzyme expression affect Busulfan metabolism is critical for determining appropriate dosing regimens and ensuring optimal therapeutic efficacy while minimizing adverse effects during hematopoietic stem cell transplantation or other Busulfan-containing treatments [47].

Time-dependent pharmacokinetics (TD-PK) is when a medication's clearance or other pharmacokinetic properties change over time during therapy. This might result in non-

linear dose-to-plasma concentration relationships, necessitating careful monitoring and modifications to ensure safe and successful therapy [48]. Exposure-outcome relationships (EORs) study the relationship between a drug's exposure (e.g., area under the curve, peak concentration) and clinical outcomes (e.g., efficacy, toxicity). Understanding these connections is critical for optimizing medication therapy and customizing dose regimes.

Clinical Implications

Monitoring busulfan plasma concentrations regularly is critical to identify time-dependent changes and modify dosages accordingly. Taking patient-specific characteristics such as age, weight, and enzyme activity into account allows for personalized dosing regimens to obtain optimal exposure while minimizing toxicity risks [48]. Understanding EORs enables the construction of models that predict clinical outcomes based on medication exposure, allowing for further optimization of therapy [48].

Both TD-PK and EORs are found in Busulfan utilized in HSCT. CYP enzyme inhibition, metabolic pathway saturation, glutathione depletion, protein binding alterations, and disease development are all factors that influence TD-PK. Engraftment, toxicity, and illness recurrence are examples of EORs. Adequate busulfan exposure is required for effective engraftment, but exceeding it increases the risk of graft failure and toxicity [48].

Implications for Future Research

The research supports the potential benefits of TDM for Busulfan in HSCT; however, some significant limitations in current evidence need to be addressed. These include small sample size trials, patient population variability, insufficient long-term follow-up data, a need for standardized techniques, and economic issues. Recommendations include determining appropriate busulfan levels, implementing standardized dosage algorithms, incorporating TDM into various healthcare settings, and increasing awareness among healthcare professionals [49]. By overcoming these obstacles, we can optimize busulfan therapy and improve HSCT patient outcomes [49].

More significant, multicenter, well-designed research is needed to address these limitations and further cement the evidence for the benefits of Busulfan TDM. These studies should include more extensive and diverse patient populations, long-term follow-up to assess the impact of TDM on long-term outcomes such as overall survival and disease-free survival, standardized TDM protocols and data collection methods for better cross-study comparison, and cost-effectiveness analyses to determine the financial feasibility of implementing TDM in various healthcare settings [50].

More research should be conducted to develop enhanced TDM technologies, investigate pharmacodynamic markers, and improve patient education and involvement. We can validate and expand the current knowledge base on Busulfan TDM by addressing these areas through comprehensive research initiatives and collaborative efforts, developing standardized protocols, optimizing dosing algorithms, and establishing clear guidelines for TDM implementation in diverse clinical settings [51].

CONCLUSION

The current literature evaluation revealed good outcomes for busulfan TDM; however, extensive trials are required to demonstrate the benefit of anticipating and avoiding adverse drug reactions and sufficient dosage to reach desired objectives. Future research on TDM of busulfan-based regimens in adult HSCT patients must address several critical issues. First, research assessing how TDM-guided dosage alterations affect long-term clinical outcomes such as overall survival, relapse rates, and treatment-related morbidity would provide vital new information about the actual efficacy of tailored dosing. It is also critical for healthcare decision-makers to assess the cost-effectiveness of regularly including TDM in busulfan regimens.

Furthermore, prospective studies examining the association between busulfan intake and specific genetic variations impacting drug metabolism can help us better understand interpatient heterogeneity. Comparative studies evaluating the viability and reliability of different TDM procedures are necessary to address practical difficulties connected to TDM, such as ideal sample intervals and appropriate assay methodologies. Finally, research should focus on developing standard recommendations for using TDM in various clinical scenarios to enhance consistency in practice. When these considerations are considered, busulfan-based HSCT methods will improve, as will patient outcomes.

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