Busulfan Used in Leukanemia Cancer

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***Abstract*—The early history of leukemia reaches back 200 years. In 1811, Peter Cullen defined a case of splenitis acutus with unexplainable milky blood. Early signs of leukemia in blood work often include abnormal blood cell counts, particularly high or low white blood cell counts, low red blood cell counts, and low platelet counts. These abnormalities can be detected through a complete blood count (CBC) test, which is a common initial diagnostic test for leukemia. However, not all leukemia types cause these cells to circulate in the blood; they may remain in the bone marrow. For the treatment of leukemia, we use the anticancer drug that is busulfan. Busulfan was approved by the US Food and Drug Administration (FDA) for treatment of chronic myeloid leukemia (CML) in 1999. Busulfan is a type of chemotherapy drug that works by damaging the DNA inside cells, also stop cancer cell growth. It's used to treat leukemia and prepare for bone marrow transplants. The therapeutic monitoring of busulfan is often initiated to ensure that the patient's level is within the optimal goal range. For patients over 12 kg, use busulfan injection at 0.8 mg/kg intravenously every 6 hours for 4 consecutive days (Days -7, - 6, -5, and -4), followed by cyclophosphamide at 60 mg/kg intravenously on Days -3 and -2. Busulfan specifically works by having a hydrolysis reaction occur with the 2 easily displaced methane sulfonate groups located on opposite ends of a butane chain within the drug's chemical structure. This is a nucleophilic substitution reaction with the guanine molecules to create positively charged, highly reactive carbonium ions. These ions form DNA intra strand cross- links, which, in turn, disrupt and damage the cancer cell's DNA. Another inhibitory effect that busulfan exerts on DNA is binding to the cysteine molecules of histone proteins, which leads to DNA-protein binding. Busulfan also disrupts the cellular redox equilibrium by interacting with the sulfhydryl groups of glutathione, increasing oxidative stress in cancer cells.**

I. INTRODUCTION

History

Leukemia is a type of cancer affecting the blood and bone marrow, characterized by the rapid production of abnormal white blood cells[1]. These abnormal cells crowd out healthy blood cells, impairing the body's ability to fight infections[2].

Early Observations (1811–1845): First strange cases of leukemia-like illness were described. In 1845, leukemia was officially identified and named.

Developments (1845–1900): Leukemia linked to blood-forming organs like bone marrow[3]. Types of leukemia (myeloid and lymphoid) were defined.

20th Century Advances: Chromosomes linked to cancer. First chemotherapy tried in 1947.In 1960, a key genetic marker (Philadelphia chromosome) was found.

Modern Era (1976–Today): Better classification and risk-based treatments developed. Bone marrow transplants used. Genetic research improved diagnosis and led to targeted drugs like imatinib. Research is still ongoing for better treatment[4].

RATIO IN POPULATION

LEUKEMIA NEW CASES: In 2024, 62,770 people are expected to be diagnosed with Leukemia.

PREVALENCE: An estimated 456,481 people are living with or in remission from leukemic in the US.

SURVIVAL: The 5-year relative survival rate for leukemia has more than doubled, from 34 percent for 1975 to 1977 to 70 percent for 2013 to 2019[5]. From 2013 to 2019, the 5-year relative survival rates overall were

ALL – 71.3 percent overall, 92.1 percent for children

and adolescents younger than 15 years, and 93.5 percent for children younger than 5 years
AML – 31.7 percent overall and 68.8 percent for children and adolescents younger than 15 years
CLL – 88.0 percent overall
CML – 70.6 percent overall
Deaths
Approximately 23,670 deaths (13,640 males and 10,030 females) in the US are expected to be attributed to leukemia in 2024[6]. From 2016 to 2020, leukemia was the sixth most common cause of cancer deaths in males and the seventh most common cause of cancer deaths in females in the US. Dietary intake data were collected from 81% of participants (n = 640). We found that 27% of participants were overweight/obese[7]. Intake of total calories and other nutrients exceeded the dietary reference intake in up to 79% of children. This was evident in both risk groups and was pronounced among younger children[8]. For micronutrients, dietary intake of calcium, vitamin D (females only), and zinc differed significantly between patients with standard-risk and those with high-risk ALL.

II. DRUG PROFILE:

Busulfan is bifunctional alkylating agent used to treat chronic myelogenous leukemia[9].

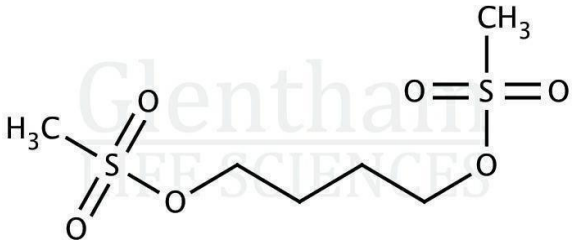


FIGURE NO.1 STRUCTURE OF BUSULFAN DRUG

IUPAC NAME: 1,4-Butanediol di-methane-sulfonate is made by reacting butandiol with methane-sulfonyl chloride[10].

BRAND NAME: Myleran, Busulfan Fresenius Kabi, Busulfex. Generic Name: Busulfan

ROUTE OF DRUG ADMINISTRATION**:** Oral, I.V. [11]

III. MARKETED PREPARATION:

Marketed preparation of busulfan for I.V. administration

TABLE NO. 1

Formulation	Brand/Trade Name	Strength	Notes
Injection (IV)	Busilvex® / Busulfex®	6 mg/mL (10mL or 60 mL vials)	Given as infusion; widely used in hematopoietic stem cell transplantation (HSCT).

Marketed preparation of busulfan for Oral Administration

TABLE NO. 2

Oral tablets	Myleran® (original brand), Busilvex®, Busulfex®, generic forms	2 mg tablets	Historically most common; used in chronic myeloid leukemia (CML) and pre-transplant conditioning.

PRODUCT ORIGIN**:** Scientists: A. Haddow and G. M. Timmis. Year of synthesis: 1953. First clinical use: Late 1950s in CML. IV formulation available: 2000[12].
WEIGHT
AVERAGE: 246.302
MONOISOTOPIC:246.02317956 Molecular formula: $C_6H_{14}O_6S_2$
MOLECULAR WEIGHT: 246.30 g/mol
MELTING POINT: 114 – 118°C
VOLUME OF DISTRIBUTION: The median volume of Distribution of Busulfan was calculated to be 500 – 1500 ml/kg[13].

PROTEIN BINDING:
The Busulfan is approximately 32.4% and 47% bound to red blood cells[14].

SUMMARY TABLE NO. 3

Binding Type	Approximate Fraction
Irreversible (Plasma proteins	~32%
Reversible (Plasma Proteins)	~7%
Total Plasma Protein Binding	~39%

Half-life: 2-3 hours

SHELF LIFE: TABLE NO. 4

Formulation	Storage condition	Shelf life
Busulfan Tablets	Store at room temperature (20 -25°C), protect from moisture.	2-3 years (as per manufacture's expiry

TABLE NO. 5

Formulation	Storage condition	Shelf life
Busulfan Injection (IV, eg., Busilvex)	Unopened vials: store in refrigerator (2-8°C).	3 years
After dilution for infusion (with 0.9% NACL or 5% dextrose)	Stable at room temperature (≤25°C) for up to 8 hours, or in refrigerator (2-8°C) for up to 12 hours (Including infusion time)	Use immediately when possible

CLEARANCE:

Busulfan clearance scaled to BSA (typical value, 5.47 L/[h•m^2]) is more uniform across the pediatric age span, except for infants (≤ 1 year, 4.27 L/[h•m^2])[15].

SOLUBILITY:

Busulfan is considered poorly soluble in water, with a soluble around 0.1g/L, but soluble in certain organic compounds like dimethylformamide, N, NN di-methyacetamide DMA), DMSO, and polyethylene glycol 400(PEG400)[16].

BIOAVAILABILITY:

Between 60% - 80% Bioavailability of Busulfan by oral administration Variable between patients due to absorption and first-pass metabolism. Food has little effect, but consistency is recommended. IV 100% Direct delivery, avoids variability. Used especially in conditioning regimens before bone marrow transplant[17].

III. PHARMACOKINETICS OF BUSULFAN[18]

ABSORPTION: Oral absorption is less & varies by dose, age and disease. So, the oral administration variable oral bioavailability. I. V. Preferred for consistency.

DISTRIBUTION: It binds with plasma protein (30% - 32%) and cross the blood brain Barrie (BBB), reaches the brain, causing possible side effect.

METABOLISM: Busulfan mainly broken down in liver through glutathione (a natural body chemical).

ELIMINATION**:** Mostly removed as other substances. Very little unchanged drug excreted through kidney in form of urine.

IV. PHARMACODYNAMICS OF BUSULFAN[19]

CLASS & MECHANISM OF ACTION**:** Belongs to the alkyl sulfonate class of alkylating agents. Busulfan forms covalent bonds with DNA by alkylating the N7 position of guanine bases. This leads to DNA cross-linking (intra- and interstrand) → blocks DNA replication and transcription → induces apoptosis.

It is cell cycle–non-specific, but its effects are most pronounced in rapidly dividing cells.

THERAPEUTIC EFFECTS**:** Causes profound myeloablation (suppression of bone marrow) → reduces immune system activity. This property makes it especially useful in conditioning regimens before bone marrow or stem cell transplant, to eliminate host hematopoietic cells and create space for donor stem cells.

SELECTIVITY: Not selective for malignant cells → damages normal rapidly dividing cells as well (bone marrow, GI tract, hair follicles).

ONSET AND DURATION**:** Produces cumulative cytotoxic effects after repeated dosing. Myelosuppression typically develops within 7–14 days of administration.

V. ADVERSE DRUG REACTION

Impact of acetaminophen (Tylenol): Acetaminophen also uses glutathione to be metabolized. If taken

within 72 hours before or after busulfan[20], it can reduce glutathione levels, slowing down busulfan clearance. This can cause higher levels of busulfan in the blood, increasing the risk of side effects.
Recommendation: Avoid acetaminophen around the time of busulfan treatment.
Impact of phenytoin: Phenytoin increases the liver's ability to clear busulfan, leading to lower busulfan levels.

TOXICITY (OVERDOSE SIGNS): If someone takes too much busulfan, warning signs may include: Allergic reaction (rash, swelling, or trouble breathing), Easy bleeding or bruising, feeling very weak or unusually tired, Ongoing cough, chest congestion, or trouble breathing, Pain in the stomach, sides (flank), or joints, Severe nausea, vomiting, or diarrhea, Dizziness, confusion, or darkening of the skin, Fever, chills, or sudden collapse and Loss of consciousness[21].

DRUG FOOD INTERACTIONS:
In simple the interaction between drug and food. Drug-food interactions occur when food or beverages affect how a medication works in the body.

DRUG INTERACTIONS
TAKE AT THE SAME TIME EVERY DAY: Consistent timing helps maintain stable levels of the medication in your body and improves effectiveness.

DRINK PLENTY OF FLUIDS: Staying well-hydrated supports the effectiveness and absorption of many medications.

MECHANISM OF ACTION
Busulfan is a bifunctional alkylating agent of the alkyl sulfonate class. It contains two unstable methane sulfonate groups that, upon hydrolysis in aqueous environments, are released and form a reactive carbonium ion. This ion alkylates DNA, thereby exerting its cytotoxic effect. Busulfan has limited solubility in water; however, an intravenous formulation was introduced in 2000. Initially, busulfan was used in the palliative treatment of chronic myeloid leukemia (CML) due to its strong myelosuppressive properties[22].

DNA Double Helix

↓

Alkylating Agent (e.g., Busulfan)

↓

Formation of Aziridinium Ion

↓

Alkylation of DNA Base (mainly Guanine at N7 position)

↓

Cross-linking of DNA Bases (A-T / G-C pairs) (Baxter, 2013GlaxoSmithKline, 2003)

↓

Increase DNA Fragmentation

↓

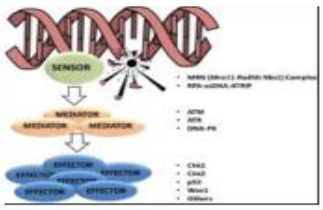
Increase NA Damage

↓

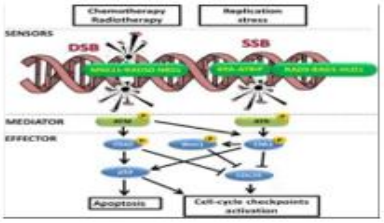
Inhibition of DNA Replication & Transcription

↓

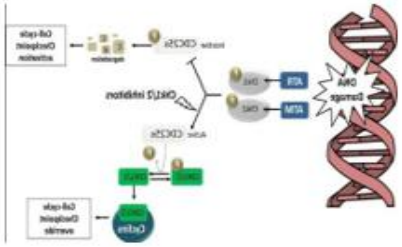
Stop Cancer Cell Growth



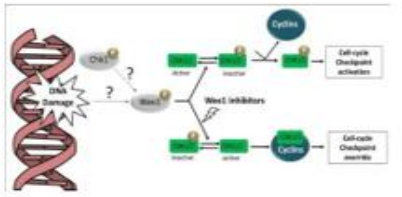
1. Schematic representation of DNA damage response (DDR)



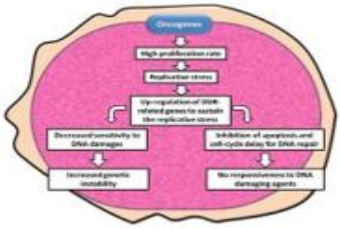
2. Plasma time-concentration curve after 3.03 mg intravenous (e) and 2 mg oral administration (A) of busulfan



3. Schematic representation of the mechanism of action of CHK1/CHK2 inhibitor.



4. Schematic representation of the mechanism of action of the WEE1 inhibitor.



The DDR pathway in cancer cells.

FIGURE NO. 2: THE CELL CYCLE CHECKPOINT INHIBITORS IN THE TREATMENT OF LEUKEMIAS

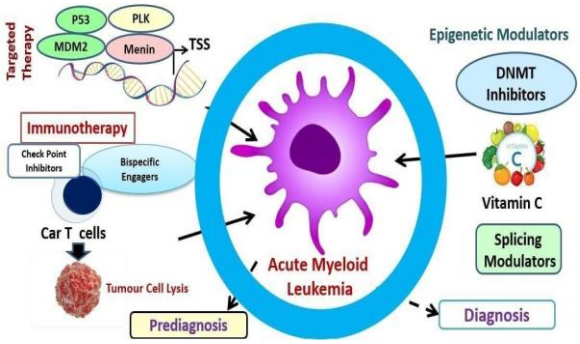


FIGURE NO.3: CELL TARGETING OF LEUKEMIA

Clinical Trials Data
Bioavailability Study of Busulfan
Busulfan is used in bone marrow transplantation.

CHILDREN VS ADULTS:
Children show wider variation in oral bioavailability (0.22–1.208) than adults (0.47–1.03)[23].

Half-life (IV) similar (children ~2.5 h, adults ~2.6 h).
Clearance (per kg): higher in children (3.62 vs 2.49 mL/min/kg).

VOLUME OF DISTRIBUTION (PER KG): higher in children (0.74 vs 0.56 L/kg). When normalized to body surface area (BSA), clearance differences disappear → dosing should be based on BSA, not weight. Because bioavailability is highly variable, therapeutic drug monitoring (TDM) and dose adjustment are important to avoid toxicity or graft failure. In short, Children metabolize and distribute busulfan differently, so dosing by BSA and careful monitoring is recommended[24].

VI. MATERIAL AND METHODS

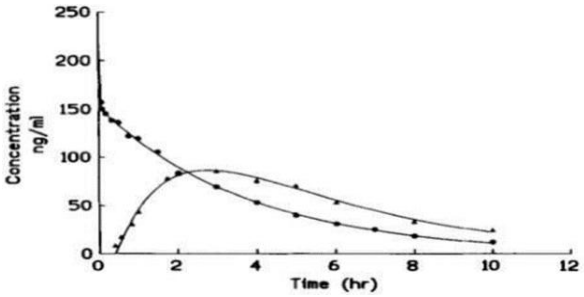
PATIENTS: Eight children with median age of 1.5 years and eight adults (seven adults and one older child with median age 43 years) undergoing BMT took part in the study.
Dosing:
Day 1 → 2 mg IV busulfan.
Day 2 → 2 mg oral busulfan.
Day 3 → high-dose therapy (1 mg/kg every 6 hrs. ×

16 doses).
Drug preparation: freshly made, sterile, stable only a few hours, stored at 4°C. Sampling: Blood collected up to 10 hrs. after dosing; plasma stored at –20°C[25].

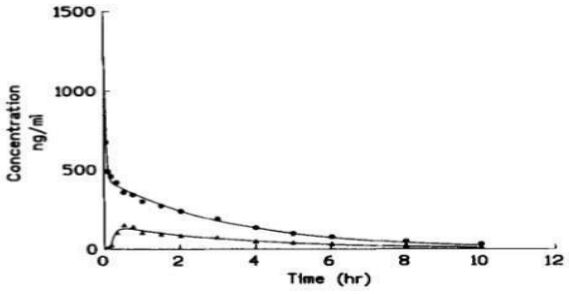
ANALYSIS
Method: Gas chromatography with electron capture.
Models: IV data → 2-compartment; Oral data → 1-compartment. Parameters measured: absorption constant (ka), elimination constant (ke), distribution volume (Vdss), lag time, AUC.
Stats: Student's t-test, regression with age, bioavailability from AUC (IV vs oral).

RESULTS
Clearance (per kg): higher in children (3.62 vs 2.49 mL/min/kg). Clearance (per BSA): no difference between groups.
Half-life: similar (children ~2.5 h, adults ~2.6 h).
Distribution volume (per kg): higher in children (0.74 vs 0.56 L/kg).

AUC: wider in children (309–1510) vs narrower in adults (103–270).



GRAPH NO.1: PLASMA TIME-CONCENTRATION CURVE AFTER 2 MG INTRAVENOUS (E) AND 2 MG ORAL ADMINISTRATION (A) OF BUSULFAN (PATIENT EO WITH 100% BIOAVAILABILITY)[26].



GRAPH NO.2: PLASMA TIME-CONCENTRATION CURVE AFTER 3.03 MG INTRAVENOUS (E) AND 2 MG ORAL ADMINISTRATION (A) OF BUSULFAN (PATIENT LS WITH BIOAVAILABILITY OF 52%)[27].

VII. PROBLEM ASSOCIATED IN PATIENT WITH BUSULFAN

1. Gastrointestinal issues – nausea, vomiting, diarrhea, mouth sores.
2. Fertility problems – can cause permanent infertility in both men and women.
3. Secondary cancers – long-term use may increase risk of other malignancies.
4. Other symptoms – fatigue, dizziness, fever, pain in joints or stomach, and allergic reactions.
5. Bone marrow suppression (myelosuppression) – major effect; leads to low blood cell counts (anemia, infections, bleeding tendency).
6. Pulmonary toxicity (Busulfan lung) – progressive lung damage (fibrosis), causing cough and breathing difficulty.
7. Hepatic toxicity – can cause veno occlusive disease (VOD), especially with high doses or transplant conditioning.
8. Seizures – at high doses; often prevented with anticonvulsants during therapy.
9. Skin changes – darkening of the skin (hyperpigmentation).

VIII. TREATED LEUKEMIA BY USING BUSULFAN DRUG

TYPE OF LEUKEMIA TREATED: Busulfan was mainly used in the palliative treatment of chronic myeloid leukemia (CML) before the advent of newer targeted drugs (like imatinib).

HOW IT WORKS: Busulfan is an alkylating agent that damages DNA in rapidly dividing cells, including leukemia cells. This slows down or stops their growth.

ROLE TODAY: Busulfan is now less commonly used for direct leukemia treatment. Instead, it is widely used as part of conditioning regimens before bone marrow or stem cell transplantation in patients with leukemia (CML, AML, ALL).

IX. CONCLUSION

This study suggests the Busulfan is bifunctional alkylating drug is most powerful anticancer drug as compared to other anticancer drugs and it plays important role in the therapeutic management of leukemia, especially in Chronic Myeloid Leukemia (CML). It inhibits the DNA synthesis by cross linking the DNA base pair and bone marrow function, allowing donor cells to engraft. Busulfan drug necessary in conditioning regimens before hematopoietic stem cell transplantation, its direct usage as a frontline therapy has decreased with the introduction of targeted medications such as imatinib.

A bifunctional alkylating agent was known busulfan has been critical in the three peutic management of leukemia, especially chronic myeloid leukemia (CML). B usulfan continues to necessary in conditioning regimens before hematopoietic s tem cell transplantation, even if its direct usage as a frontline therapy has decrea sed with the introduction of targeted medications like imatinib. Its DNA crosslinking technique accurately inhibits bone marrow function, allowing donor cells to engraft. However, cautious therapeutic medication monitoring is required due to variable bioavailability, toxicity threats. and long-term consequences. All things considered, busulfan remains a mainstay in transplant. based leukemia treatment, striking a balance between effectiveness and risk of side effects.

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