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# ANTINEOPLASTIC AGENTS USED IN PEDIATRIC HEMATOPOIETIC BONE MARROW TRANSPLANTATION: A REVIEW ABOUT PHARMACOLOGY AND PHARMACEUTICAL ISSUES

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## ABSTRACT

This article proposes the characterization of the main chemotherapeutic agents used in hematopoietic stem cell transplantation in pediatric patients, carrying out a review of the main pharmacological and pharmacokinetic characteristics that are peculiar to children, as well as technical aspects for the handling, prescription, and administration of each one of these.

It is extremely important that all professionals know how to recognize the characteristics of each drug and how its peculiarities impact the quality of patient's treatment, being able to predict and propose necessary interventions for potential problems of therapy, which can be identified and measured.

**Keywords:** Chemotherapy. Chemotherapeutic agents. Bone Marrow Transplantation. Pediatrics.

## 1. INTRODUCTION

The indication for hematopoietic stem cell transplantation (HSCT) in pediatrics presents peculiarities, since there are a greater number of indications in non-malignant diseases and a greater chance of cure in hematological neoplasms, thus making it possible to carry out many combinations of chemotherapeutic agents for the elaboration of protocols. Moreover, the pharmacokinetics of chemotherapeutic agents may differ from the way they occur in adults.

In this scenario, studies reported and going on in the Pediatric Pharmacology using these drugs should be highlighted, since important differences are observed in comparison to adults in their pharmacodynamics and pharmacokinetics.<sup>1</sup> Important aspects of the pharmacology of these agents in children are related in pharmacokinetics aspects, which have

a greater impact on distribution and metabolism phases than on absorption and excretion phases.

The absorption phase of the drug can suffer significant changes if administered per oral once the drug passes through the mouth, stomach or intestinal absorption, which can be affected by gastrointestinal motility, gastric pH and conveyors.<sup>2</sup> For instance, in oral absorption, we evaluate changes in development phase, mainly related to: acid secretion, gastrointestinal motility and biliary secretion. Usually, these changes are smaller at birth and after 6 or 8 months of life, thus, it may interfere in the reduction or delay of absorption.<sup>2</sup> In distribution phase, which the most of chemotherapeutic agents are already available, factors such as aqueous or lipid components, plasma proteins and carriers are essential for evaluation during developmental changes phase.<sup>2</sup>

The amount of extracellular fluid is greater at birth and with the arrival of youth, this factor is reduced, causing a greater distribution volume in children (smaller concentration peaks); the protein binding rate is also lower at birth but increases significantly up to 1-2 years of age; the permeability of the blood-brain barrier is much higher at birth, so that after 3 years of age, this barrier permeability is already similar to adults.<sup>2</sup>

After distribution there is a metabolism phase, usually in the liver, going through two enzyme phases. Phase I enzymes such as CYP450 (CYP3A4, 2D6, 2C8/9...) are in smaller quantities at birth and they increase to adult levels during childhood and youth, while phase II enzymes, such as glucuronides, glutathione, sulfates, and acetates reach levels compared to adults after 6 months of life.<sup>2,3</sup>

In the excretion phase, in which the kidney is the main drug excreting organ, the maturation of this organ begins in the embryo and is completed in childhood. Glomerular filtration rates reach adult values between 6 months to 1 year old. In general, it was observed expressive changes in children and youth with pre-existing comorbidity which can increase the risks of toxicity.<sup>4</sup>

Chemotherapy drugs often have a narrow therapeutic window and combined with a large variability between drug plasma concentrations observed in pediatric oncology patients, this can result in suboptimal therapy or increased toxicity.<sup>5</sup>

In clinical practice, physiologic characteristics, pharmacokinetics profile, and rational drug prescription are decisive for the success of the transplant.

To help physicians, pharmacists and nurses to perform the best therapy for the patient, it is described below the main chemotherapeutic agents used in mobilization and conditioning protocols. This discussion includes granulocyte colony-stimulating factor Filgrastim (G-CSF), with description of clinical, pharmacodynamic and pharmacokinetic aspects, emetogenic potential and recommended dose adjustments for renal or hepatic toxicity. In order to demonstrate clearly and objectively, technical aspects such as compatibilities, concentration, irritant potentials, needed care in administration, as well as guidance and drug characteristics for handling are compiled in a table (see Table 1), organized based on their alphabetical names.

## 2. ALKYLATING AGENTS

### 2.1 Busulfan

It is a bifunctional alkylating agent, that has a mechanism of action based on the release of methane-sulfonate groups, producing carbon ions which can insert an alkyl group in the DNA strand. It is used in conditioning regimens in association with other drugs, such as melphalan, cyclophosphamide and fludarabine.<sup>6,7</sup>

The volume of distribution (Vd) ranges between 0.62 and 0.85 L/kg. It is mainly metabolized in the liver. About 30% of the administered dose is excreted in the urine over 48 hours with 1% of the drug in unchanged form.<sup>6</sup>

When administered orally, the bioavailability of busulfan is quite variable, so there is a preference for the intravenous route. Busulfan clearance is related to age (the higher the age, the lower the clearance) and weight (the higher the weight, the lower the clearance). For patients older than 18 years, clearance ranged from 2.64 to 2.9 mL/min/kg. For children aged from 2 to 14 years, it ranged from 4, 4 to 4.5 mL/min/kg and for children aged 3 years or less, clearance ranged from 6, 8 to 8.4 mL/min/kg.<sup>6</sup>

Busulfan has moderate to high emetogenic potential (>30-90% emesis frequency) at doses used in the conditioning regimen. They can cause epileptic seizures, which can occur up to 24 hours after the last dose of busulfan, due to their high lipid solubility and low level of protein binding. Thus, the prophylactic use of anticonvulsants is indicated for at least 12 hours before the first dose of busulfan, and for at least 24 hours after the last dose infusion. The most used drug for prophylaxis is phenytoin, but caution is needed in its administration because phenytoin increases busulfan clearance by  $\geq 15\%$ . If alternative anticonvulsants are used, busulfan clearance may be decreased and dosing should be monitored accordingly.<sup>8</sup>

For both intravenous and oral administration, it is recommended to monitor the serum level of busulfan to reach the desired levels (concentration between 200 to 600 ng/mL), thus avoiding possible toxicities. Busulfan doses can be adjusted according to serum level (according to protocol and disease).<sup>6</sup>

An adverse effect often associated with busulfan conditioning regimens is Sinusoidal Obstruction Syndrome (SOS). It usually occurs within the first 30

days of transplantation, with an incidence of 5 to 40% in pediatric patients.<sup>9</sup> For treatment, defibrotide is usually used in adults and children. The use of acetaminophen should be avoided due to the risk of SOS.<sup>8,9</sup>

There are no cases in literature about dose adjustment to renal or hepatic impairment.

## 2.2 Carmustine

Alkylating agent from nitrosourea family, their cytotoxic action is mediated by the inhibition of enzymatic processes involved in DNA formation. This drug also causes a break in DNA strands and, consequently, processes in the synthesis of DNA, RNA, and proteins were changed. It has a Vd of 3.25 L/kg and liver metabolism (not specified). Their excretion is mostly renal (60% to 70%), but it can also be excreted through the respiratory (6 to 10%) and fecal (1%) routes. Their elimination half-life is of 22 minutes (1.4 minutes in the primary phase and 17.8 minutes in the secondary phase), and the emetogenic potential ranges from high (when > 250mg/m<sup>2</sup>) to moderate (when < 250mg/m<sup>2</sup>). It is used in autologous HSCT in the conditioning phase in myeloablative schemes, such as BEAM and BEAC.<sup>8</sup>

## 2.3 Cyclophosphamide

Cyclophosphamide is an alkylating agent of the oxazaphosphorine class. With activation in the liver based on two cytotoxic metabolites: phosphoramidate mustard and acrolein, knowing as a pro-drug. Their antineoplastic activity is linked only to phosphoramidate, which binds to the DNA of the tumor cell, which in turn, does not interrupt the production of RNA and proteins. Therefore, an imbalance occurs, leading the tumor cell to death. Despite they have not an antineoplastic effect, acrolein is responsible for the urotoxic side effects of cyclophosphamide, treated prophylactically with mesna (65 to 100% of the cyclophosphamide dose) for uroprotection.<sup>10,11,12</sup>

Constant hydration is also essential, to help the stimulate bladder emptying at regular intervals, and their administration should be avoided at night to prevent urinary retention and increase the amount of toxic active metabolites that would remain in the bladder for longer. It is also important to monitor urinary sediments that may be signs of urotoxicity or nephrotoxicity.<sup>13</sup>

It has moderate emetogenic potential for doses less than or equal to 1500 mg/m<sup>2</sup> and high emetogen-

ic potential for doses greater than 1500 mg/m<sup>2</sup>, so the use of antiemetics is recommended. Stomatitis and mucositis can also be manifested with the use of protocols containing cyclophosphamide.<sup>8</sup> Their plasma concentration varies according to the dose administered. The peak concentrations are 4, 50 and 500 nmol/mL after administration of 1 to 2 mg/kg (Peters et al, 1989), 6 to 15 mg/kg (Klein et al, 1980) and 60 mg/kg (Jardine et al, 1978), respectively.<sup>10,11,12</sup>

A delay in cyclophosphamide metabolization may occur in patients with liver failure. Importantly, it is a drug that crosses the placental barrier and is detectable in breast milk and cerebrospinal fluid. It is mainly excreted by the kidneys and it is indicated to change the dose in cases of renal failure. It has a half-life of approximately 7 hours in adults and 4 hours in children, with peak levels of alkylation occurring within about 2 to 3 hours of drug administration. For cases where creatinine clearance is less than 10 mL/minute, administer 100% of the dose, and if it is greater than or equal to 10 mL/minute, adjust to 75% of the initial dose.<sup>8</sup>

## 2.4 Melphalan

Alkylating agent that inhibits DNA and RNA synthesis via interstrand cross-linking with DNA, binding at the N7 position of guanine.<sup>8</sup>

It is a mechlorethamine derivative that stops the DNA replication process, leading to cell death. High dosage melphalan treatment is associated with side effects such as oral mucositis. To reduce the incidence of these side effects, it is recommended pre and post melphalan cryotherapy for patients who will receive high doses of the drug, which can also be performed with ice cubes. In addition, a high volume of hydration is recommended to avoid precipitation of melphalan in the renal tubules.<sup>13</sup>

Regarding pharmacokinetics, their Vd is 0.5 L/kg, and it binds to plasma proteins, mainly to albumin (55-60%). It has limited penetration of the blood-brain barrier and its excretion is fecal (20-50%) and renal (10%). Melphalan is not a dialyzable drug. Its elimination half-life is of 90 minutes, so the drug infusion should not pass this period. It has a high emetogenic potential (at doses > 140 mg/m<sup>2</sup>) and moderate (at doses < equal 140 mg/m<sup>2</sup>).<sup>10</sup>

At autologous stem cell transplant, if the serum creatinine was up then 2 mg/dL, a reduction of up to 30% of the programmed initial dose is recommended.<sup>8</sup>

## 2.5 Thiotepa

Thiotepa is a stable aziridinium compound that has activity in initial and metabolite forms, thiotepa (triethylenethiophosphoramidate) triethylenephosphoramidate (TEPA), respectively. It has activity against some solid tumors but, today it is reserved for some specific cases of conditioning with high doses of chemotherapy in HSCT. Their mechanism of action consists of the protonation of the nitrogen of the aziridinium group, leading to its instability and causing a consequent nucleophilic cross attack on the DNA strands.<sup>14</sup>

In pediatric HSCT doses vary between 125 mg/m<sup>2</sup> and 350 mg/m<sup>2</sup> in 2 to 3 subsequent days of infusion (autologous and allogeneic) and should not exceed the maximum cumulative dose of 1050 mg/m<sup>2</sup> or 42 mg/kg.<sup>15</sup>

The plasma half-life varies between the two active forms, taking from 03 to 21 hours. Excretion is performed by both the kidneys and liver. It does not require dose adjustment in renal and hepatic dysfunctions (however, the risks must be less than the clinical benefits, and its use is contraindicated in severe insufficiencies) and these characteristics occur in the same way in adults and children.<sup>14,16</sup>

This drug can cause mucositis, SOS, hepatotoxicity, neurotoxicity and pneumonitis. It has a dose-dependent emetogenic potential (moderate at doses < 300 mg/m<sup>2</sup>; high at doses ≥ 300 mg/m<sup>2</sup>).<sup>16</sup>

The use of thiotepa may be contraindicated with existing renal or hepatic impairment and should be limited to cases where benefit outweighs risk.<sup>8</sup>

## 3. ANTIMETABOLITES

### 3.1 Methotrexate

It belongs to the class of folate antagonists, acting at three different sites: inhibiting dihydrofolate reductase (DHFR) and thymidylate synthase and altering reduced folate transportation. At low doses, it is used as prophylaxis for graft versus host disease (GVHD) due to its immunosuppressive activity, probably because of the inhibition of lymphocyte multiplication.<sup>17</sup>

The usual dose for children aged two years or older is of 8 to 15mg/m<sup>2</sup> intravenously on D1, followed by 8 to 10mg/m<sup>2</sup> intravenously on D3, D6 and D11 after HSCT.<sup>18</sup>

For the handling of small doses used in protocols for GVHD prophylaxis, it is recommended to use the

commercial presentation of 25 mg/mL, thus obtaining a slightly larger volume for administration.<sup>18</sup>

The Vd is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight). About 50% of the administered dose is bound to plasma proteins. The main route of elimination is renal, with 80% to 90% of the dose being excreted in the urine within 24 hours of administration. Biliary excretion is 10% or less. Half-life for low doses is of 0.7 to 5.8 hours.<sup>18</sup>

Methotrexate is metabolized by oxidation, its main drug interactions occur by reducing renal clearance, thus increasing exposure to the drug and its possible toxicities.<sup>19</sup> It has low emetogenic risk.<sup>20</sup>

### 3.2 Cytarabine

It is an antimetabolite, cytosine analogue, a pyrimidine nucleotide. Their main mechanism of action occurs through the inhibition of DNA polymerase by competition with deoxycytidine triphosphate, causing the inhibition of DNA synthesis. It is a cycle-specific drug that acts in the S phase, and it can also block the progression of the cell cycle from the G1 phase to S phase. Its toxicity is dependent on both the drug concentration and the time of exposure. Its main cytotoxic effects are due to drug incorporation into DNA and RNA chains.<sup>21</sup>

Cytarabine is used in myeloablative conditioning. Its emetogenic risk is dose-related, with a dose of 75mg/m<sup>2</sup> having moderate risk and doses above 3000mg/m<sup>2</sup> presenting high risk.<sup>15</sup>

The drug is 13% bounded to plasma protein. It is metabolized in the liver by deoxycytidine kinase and other nucleotide kinases to the active metabolite, aracytidine triphosphate. About 86% to 96% of the dose is metabolized as inactivated form, uracil arabinoside.<sup>15</sup> It is also metabolized, in a small proportion, in the kidneys, gastrointestinal mucosa, granulocytes, and other tissues that contain the enzyme cytidine deaminase.<sup>21</sup>

Initial elimination half-life is from 7 to 20 minutes and the final one is from 1 to 3 hours. About 80% of the administered dose is renally excreted, and 90% is converted in inactive form within 24 hours.<sup>15</sup>

Some guidelines have been used by clinicians, with dosing adjustment in renal impairment only in high-dose cytarabine (≥ 2000 mg/m<sup>2</sup>/dose) for serum creatinine 1.5 – 1.9 mg/dL or increase of 0.5 – 1.2 mg/dL, reducing dose to 1000 mg/m<sup>2</sup>/dose.<sup>8</sup>

Dosing adjustment for hepatic impairment is recommended to patients with liver failure since cytarabine

is partially detoxified in the liver. The recommendation of authors such as Floyd, 2006 is to reduce the dose by 50% for any increase in transaminases, and subsequent doses can be increased in the absence of toxicity.<sup>8</sup>

### 3.3 Fludarabine

It is a fluorinating nucleotide analogue to antiviral agent vidarabine. It is a water-soluble prodrug that is converted to the active 2-fluoro-ara-ATP by the enzyme deoxycytidine kinase. This metabolite competitively inhibits DNA synthesis through the inhibition of DNA polymerase, ribonucleotide reductase, DNA primase, and DNA ligase. Its action occurs mainly in the S phase of the cell cycle.<sup>15,22</sup>

It is used in conditioning regimen for reduced-intensity allogeneic transplantation with a dose limited to 30mg/m<sup>2</sup>, once a day, for 6 doses. It can be used in combination with busulfan and thymoglobulin for hematologic malignancies or in association with busulfan and alemtuzumab in myeloid neoplasms and in non-malignant diseases. It has minimal emetogenic potential.<sup>23</sup>

Fludarabine Vd is of 83-98L/m<sup>2</sup>. The active metabolite is quickly and totally dephosphorylated in plasma to the inactive metabolite, 2-fluoro-ara-A. The elimination half-life is of 10.5 to 19 hours. About 40 to 60% is excreted in the urine, with 23% as 2-fluoro-vidarabine within 24 hours. Renal elimination is dose dependent, being of 24% at doses of 25mg/m<sup>2</sup>/day and reaching 40-60% at high doses. Drug clearance is 79mL/min/m<sup>2</sup>.<sup>15</sup>

Adjustment of the dose for renal impairment in infants, children and youth is recommended if the glomerular filtration rate (GFR) is between 30-50 mL/minute/1.73m<sup>2</sup>, opting for the administration of 80% of the dose and if GFR <30 mL/minute/1.73m<sup>2</sup> is not recommended.<sup>8</sup>

### 4. Epipodophyllotoxins - Etoposide

It is a semi-synthetic derivative from podophyllotoxin, a plant product with antimetabolic action. It inhibits DNA topoisomerase II, thus interrupting DNA synthesis by binding to the DNA-enzyme complex, preventing enzyme repair and consequently propagating strand breaks. Through the action of p53, these strand breaks signal the interruption of the cell cycle and when there are many, induce apoptosis. It mainly affects the S and G2 phases of the cell cycle.<sup>24,25</sup>

Their Vd is of 5 to 10L/m<sup>2</sup> and its binding to plasma proteins is 94% to 98%. It is metabolized by liver,

via CYP3A3 and 3A5, generating several metabolites. Its terminal half-life is of 6 to 8 hours, considering normal liver and kidney functions. About 55% is eliminated by urine as unchanged form within 24 hours.<sup>26,27</sup>

Adjustment of the dose for renal impairment in infants, children and adolescents is recommended if the glomerular filtration rate (GFR) is between 10 - 50 mL/minute/1.73m<sup>2</sup>, opting for the administration of 75% of the dose and if GFR < 10 mL/minute/1.73m<sup>2</sup>, opting for the administration of 50% of the dose.<sup>8</sup>

In hepatic impairment, administer 50% of dose if bilirubin between 1.5 – 3 mg/dL or AST > 3 times, and 25% of dose if bilirubin > 3 mg/dL.<sup>8</sup>

In allogeneic conditioning protocol for acute lymphoid leukemia, it is used in association with fludarabine and busulfan from 6 months of age, at a dose of 20mg/Kg.<sup>18</sup> It has low emetogenic potential.<sup>26</sup>

## 5. Biological products

Some agents from biological origin can be used both in HSCT conditioning regimens for the prevention of GVHD and in support of myelosuppression arising from therapy with cytotoxic drugs that induce myeloablation. In the specific case of alemtuzumab and antithymocyte immunoglobulin (rabbit), the main activity of these agents consists of inducing an immune response against tumor cells. Regarding supportive drugs from biological origin, they act by stimulating the production of progenitors of hematopoietic stem cells so that they can act in protection against microorganisms.

### 5.1 Alemtuzumab

Alemtuzumab is a humanized anti-CD52 monoclonal antibody developed for the treatment of lymphoproliferative disorders such as chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and prevention of GVHD. It binds to CD52, a glycoprotein contained in more than 95% of lymphocytes, macrophages, monocytes, among others (but not in granulocytes, red blood cells, platelets and hematopoietic stem cells), leading to the immune system response through ADCC-type effector mechanisms (antibody-dependent cellular cytotoxicity) and CDC (complement-dependent cytotoxicity).<sup>31</sup>

The elimination half-life varies according to administration periods and manufacturer (around 11 hours after the first dose of Campath®; 6 days after the last dose of Campath®; around 2 weeks for Lemtrada®). Clearance decreases after repeated doses due to

decreased CD52 receptors in peripheral blood. No need for adjustments due to kidney and liver failure. Furthermore, like most monoclonal antibodies, it has minimal emetogenic potential.<sup>15</sup>

### 5.2 Antithymocyte globulin (rabbit)

Antithymocyte globulin (ATG) is used in T lymphocyte depletion as a GVHD prevention strategy in both myeloablative conditioning regimens and reduced-intensity conditioning in allogeneic HSCT. It has several formulations based on the sensitization of horses, goats and rabbits, the latter being preferable for use in this scenario.<sup>32</sup>

Their mechanism of action consists mainly in the depletion of T lymphocytes but, it also decreases B lymphocytes, Natural Killer cells and dendritic cells when administered in high doses. The proposed mechanisms of action induce cell depletion through mechanisms of ADCC, CDC, B cell apoptosis and modulation of key surface molecules such as adhesion receptors and chemokines.<sup>33</sup>

It can lead to hypersensitivity and anaphylaxis reactions, requiring premedication with corticosteroids, paracetamol, and antihistamines.<sup>15</sup> Besides that, it can induce cytomegalovirus (CMV) reactivation, requiring prophylaxis in HIV-positive patients. It can reactivate Epstein Barr virus as well and, in these cases, the physician should evaluate the use of rituximab for PTLD (post-transplantation lymphoproliferative disease) prevention.<sup>32,15</sup>

With regard of their pharmacokinetics, it can vary between adults and children. Seidel et al. demonstrated that the half-life of ATG can be constant and with a linear correlation between doses of 7.5 -20

mg/kg and Cmax, and that at high doses body accumulation of ATG may occur.<sup>34</sup>

Van Der Zilde et al. in turn, have demonstrated that ATG levels can be decreased in children due to development of anti-ATG antibodies, increasing the risk of acute GVHD.<sup>35</sup>

It does not need dose adjustment in renal or hepatic dysfunctions and has very low emetogenic potential.<sup>15</sup>

### 5.3 Filgrastim

Colony stimulating factors are used to mobilize hematopoietic stem cells from the bone marrow to the periphery, facilitating their collection for later transplantation. In addition, they are used in post-conditioning phase to promote bone marrow recovery. Among many agents in this class, we highlight filgrastim.<sup>8</sup>

Filgrastim (or G-CSF - granulocyte colony-stimulating factor) is an 18.8 kDa glycoprotein encoded by a single gene present on chromosome 17. It is produced by macrophages, monocytes, endothelial cells, among others, and generates a stimulus response from the activation of the JAK-STAT signaling pathway.<sup>36</sup> The pharmacokinetics of filgrastim indicates onset of action between 1 and 2 days after administration and normalization of neutrophil count within 4 days of use. It has a high Vd (150 mL/Kg), but no evidence of accumulation in intravenous administration. Bioavailability is around 60% and the elimination half-life in neonates is of 4.4 hours. It does not require adjustments in liver and renal failure, except in cases of filgrastim-induced glomerulonephritis, and has no emetogenic potential. The main adverse reactions of filgrastim are fever, thrombocytopenia, and bone pain.<sup>15</sup>

**TABLE 1**– Technical aspects (Drugs in alphabetical order) 8,15,17,18,21,22,23, 24,26, 27,28,29,30,37

Dosage form	Compatibility	Stability	Extravasation risk	Guidances
<b>Antithymocyte globulin (rabbit) Ampoule vial 25 mg</b>	NS or D5W	Used immediately	-	Required the use of 0.2-micron inline filter. Reconstitute with 5 mL of water for injection to a final concentration of 5mg/mL.
<b>Alemtuzumab Ampoule vial 30 mg/1mL</b>	Dilute for infusion in 100 mL NS or D5W	8 hours (15°-25°C) or 8 hours (2°-8°C)	-	Gently invert the bag to mix the solution. Do not shake the preparation prior to use.
<b>Bussulfan Ampoule vial 6 mg + 10 mL of diluent - 10 mg/mL</b>	NS or D5W to a final concentration of ≥ 0.5 mg/mL	8 hours (15°-25°C) * or 12 hours (2°-8°C) + 3 hours (15°-25°C)*	May be an irritant	Diluent volume should be 10 times the volume of bussulfan. *including infusion time.
<b>Carmustine Ampoule vial 100 mg + diluent (ethanol 3mL + 27 mL water for injection)</b>	NS or D5W	24 hours (2°-8°C) + 6 hours (15°-25°C)* or 3 hours (15°-25°C)*	May be an irritant	Incompatible with DEHP; protect from light; final concentration of 0,2-1 mg/mL; infusion over 1-2 hours. *including infusion time
<b>Cyclophosphamide Ampoule vial of 200 mg or 1000 mg</b>	NS or D5W	24 hours (15°-25°C)	May be an irritant	Urotoxic agente, recommended prophylaxis with Mesna. Reconstitute with water for injections to a final concentration of 20 mg/mL.
<b>Cytarabine Ampoule vial 100 mg/mL or 500 mg/mL</b>	NS, D5W or Ringer lactato	48 hours (15°-25°C)	-	-
<b>Etoposide Ampoule vial 20 mg/mL</b>	NS or D5W	0.2 mg/mL: 96 hours (2°-8°C) or 0.4 mg/mL: 24 hours (2°-8°C)	Irritant	Incidence of precipitation increases with final concentration > 0.4 mg/mL. Incompatible with DEHP material.
<b>Filgrastim Ampoule vial 300 mcg/1mL or prefilled syringe of 300 mcg/1mL (in this latter the volume cannot be handled).</b>	D5W	24 hours (15°-25°C) or 48 hours (2°-8°C)	-	It can be administered Subcutaneously or Intravenously, in this latter solution for administration should not exceed a final concentration of 15 mcg/mL, due to the risk of adsorption of the drug into the plastic syringe.
<b>Fludarabine Ampoule vial 50 mg</b>	NS or D5W	48 hours (15°-25°C) or (2°-8°C)	-	Reconstitute with 2 mL of water for injection to a final concentration of 25 mg/mL.

<b>Melphalan</b> Ampoule vial 6 mg + Diluent 10 mL - 6 mg/mL	NS or D5W	8 hours (15°-25°C)*or 12 hours (2°C a 8°C) + 3 hours(20°C ± 5°C)*	May be an irritant	Concentration range ≥ 0,5 mg/mL; Infusion volume can be up 10 times the volume of Bussulfan. *including infusion time
<b>Methotrexate</b> Ampoule vial 25 mg/mL or 100 mg/mL	NS or D5W	24 hours (15°-25°C)*	-	*including infusion time
<b>Thiotepa</b> Ampoule vial 15 mg or 100 mg, should be reconstituted with water for injection obtaining a final concentration of 10mg/mL	NS or D5W	8 hours (15°-25°C)* or 24 hours (2°-8°C) + 8 hours (15°-25°C)*		In pediatrics, final dilution volume must allow finl concentration between 0,5 and 1 mg/ mL; Infusion time over 2-4 hours; Mandatory the use of 0.2-micron inline filter. *including infusion time

**NS: Normal saline; D5W: 5% dextrose in water; DEHP: Di-(2-ethylhexyl) phthalate (Used in plastic bags to provide malleability); Vd: Volume of distribution.**

## CONCLUSION

The pharmacologic profile of the drugs contributed to the elaboration of a safety recommendations list of each one. The safe use of drugs in HSCT will help in guide and systematize the main actions of the drugs in therapeutic process, helping minimize the risk of errors and ensure an effective treatment, increasing patient's safety.

Knowledge of pharmacological therapy is essential for clinical practice, as it provides support for possible drug-related reactions and presents necessary

interventions for potential problems arising from the therapy, which can be identified and measured.

## CONFLICTS OF INTEREST

There are no known conflicts of interest associated with this publication.

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