Review Article

Cyclophosphamide related toxicity; A systematic review

Running Title: Cyclophosphamide related toxicity

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Abstract

Cyclophosphamide is an alkylating agent that has been used for the treatment of severe manifestations of autoimmune inflammatory disease. Cyclophosphamide is widely used for the treatment of malignancies; it exerts its impact through the cessation of cell division. Cyclophosphamide is similar to other chemotherapies and has various toxicities; however, its toxicity isn't well reported. This review was conducted to find out cyclophosphamide-related toxicities as reported in the previous studies conducted on that subject. A total of 91 articles were obtained, but only six studies were eligible for the inclusion criteria. The studies included a total number of 3531 participants. Cyclophosphamide was associated with various toxicities, including liver toxicity, urotoxicity, cardiac toxicity, hematological and non-hematological toxicities. The toxicity of cyclophosphamide varied based on the regimen and combined medications, as well as some gene variants.

Keywords: Cyclophosphamide, Toxicity, Predictors, Outcomes.

1. Introduction:

Cyclophosphamide is an alkylating agent that has been used for the treatment of severe manifestations of the autoimmune inflammatory disease since the 1960s; these inflammatory diseases include systemic sclerosis, systemic lupus erythematosus [1], rheumatoid arthritis [2], and cicatricial pemphigoid [3]. Cyclophosphamide is considered to be the strongest medication that is commonly used by rheumatologists as it has well-established efficacy [1].

Cyclophosphamide is widely used for the treatment of malignancies such as multiple myeloma [4], breast cancer [5], and renal diseases, including focal segmental glomerulonephritis and nephrotic syndrome refractory to corticosteroid [2,3,6]. It exerts its impact by stopping the cell division via cross-linking DNA strands and reducing the synthesis of DNA [7].

Cyclophosphamide is similar to other chemotherapeutic agents regarding having an increased risk for teratogenicity, secondary hematologic malignancy, sterility, and both common and opportunistic infections [1].
The toxicity of cyclophosphamide varies based on the route of administration, duration of the treatment, the dose, and cumulative dose [1, 8-14]. It can be administered by intravenous route or oral route [15]. Cyclophosphamide may result in adverse events [16]; these adverse events include sterility, amenorrhea, susceptibility to infections, suppression of bone marrow [17], nephrotoxicity, cystitis [16,17], and cardiovascular complications such as pericarditis, heart failure, sinus bradycardia, and myocarditis [18].

Cyclophosphamide acts as a prodrug, and its metabolism occurs in the liver, and it is metabolized to an active part and inactive form acrolein, which causes direct toxicity on the bladder and can cause hemorrhagic cystitis [19-21]. Acute toxicities of adjuvant chemotherapy have been well-documented by large clinical trials [22,23] and non-clinical trials [24]. However, there was a lack of studies conducted to evaluate the toxicities of cyclophosphamide. Also, there was no previous systematic analysis of the few studies conducted on that subject. So, this systematic review was performed to find out the toxicities related to cyclophosphamide by reviewing the previous studies conducted on that subject and included human subjects.

2. Method and search strategy:

Writing of this systematic review followed the PRISMA checklist guidance for systematic review and meta-analysis [25]. Exploration of PubMed and Google Scholar databases was done to obtain published scientific studies related to the current subject. The searching process involved using different keywords in order to obtain all possible articles related to the subject. The keywords used included"Cyclophosphamide, Human, toxicity, Hepatotoxicity, Cardiotoxicity, Urotoxicity, Associated toxicity." The keywords were used in various combinations to obtain all possible related studies.

2.1. Eligibility criteria:

All the titles obtained were filtered for selecting articles conducted on human subjects and excluding articles conducted on animals. The remaining findings were then reviewed for abstracts and exploring the full content to include full-text articles written in the English language. The included articles were full-text articles written in English language; these articles were then filtered to include only original articles
conducted on human subjects and focused on cyclophosphamide and excluding review articles, duplicate articles, articles with unsatisfying content such as articles not focusing on cyclophosphamide or articles with incomplete or overlapped data. Also, articles published before 2007 were excluded. So, the eligibility criteria for the included articles were articles conducted on human subjects, written in English language, available for full-text, original articles with clear data focusing on cyclophosphamide, and published after 2006. The full description of the search strategy is shown in figure 1.

Figure 1: Planning of eligible criteria

2.2. Reviewing and collecting of data:

Reviewing of data was done through reviewing the abstract and then the full articles for more details; this was followed by extraction of data of interest and transferring
the data into a specially designed excel sheet. A pre-designed table was used to collect the extracted data under specific titles.

3. Results:

This systematic review involved six studies that met the eligible criteria [26-31] (table 1).

<table>
<thead>
<tr>
<th>Author and Publication year</th>
<th>Population &amp; Sample size of participants</th>
<th>Type of Toxicity</th>
<th>Main points reported</th>
<th>Results and main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dulery et al 2021 [26]</strong></td>
<td>-Adolescents and adult population; age 15-76 years -HSCT patients -Two groups; *Patients received PT-Cy=136 *Patients who didn’t receive PT-Cy=195</td>
<td>Cardiac</td>
<td>*Incidence of early cardiac events *Major early cardiac events *The impact of PT-Cy on early cardiac events</td>
<td>* The cumulative incidence of ECE was 19% in the PT-Cy group and 6% in the no–PT-Cy group (p &lt; 0.001). * The main ECE occurring after PT-Cy were left ventricular systolic dysfunction (13%), acute pulmonary edema (7%), pericarditis (4%), arrhythmia (3%), and acute coronary syndrome (2%). * Cardiovascular risk factors were not associated with ECE. * Older age, sequential conditioning regimen, and Cy exposure before HSCT were also associated with a higher incidence of ECE. * A history of cardiac events before HSCT and ECE had a detrimental impact on overall survival; Patients who have a cardiac event after HSCT have lower overall survival. * The use of PT-Cy was associated with ECE * PT-Cy is associated with a higher incidence of ECE occurring within the first 100 days after HSCT.</td>
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<tr>
<td><strong>Campagne et al 2020 [27]</strong></td>
<td>-Infant and young children; age 0.85-85.5 months -Brain tumor pediatrics -Two groups; *Infants=42 patients≤1 year *Young patients=129 patients; 1-5 years</td>
<td>Hematological toxicities</td>
<td>*The genetic variants influence on the drug exposure *Impact of 4-hydroxy-cyclophosphamide associated toxicity</td>
<td>*Young infants (&lt; 6 months) exhibited higher mean 4OH-CTX exposure than did young children *No genotypes exhibited clinically significant influence on drug exposures *Higher 4OH-CTX was related to lower neutrophil, platelet, and hemoglobin nadirs *Worse toxicity metrics were significantly associated with higher 4OH-CTX exposures. *Decreased cyclophosphamide dosage for young infants was suggested to reduce toxicity in this population.</td>
</tr>
<tr>
<td><strong>Gadisa et al 2020 [28]</strong></td>
<td>-Adult women -Breast cancer women</td>
<td>Toxicity profile, *Hematological and non-hematological toxicities of adverse drug reactions reported for both</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Two groups; *AC regimen group=71 patients
*AC-T group=75 patients

including hematological, and non-hematological adverse reactions

AC regimen
* Hematological and non-hematological toxicities of AC-T regimen
* Predictors of hematological and non-hematological toxicities

Anticipated hematological toxicities were fatigue (98.7%), dysgeusia (97.3%), skin hyperpigmentation (96.6%), nausea (93.2%), vomiting (88.4%), gastritis (83.6%), peripheral neuropathy (74%), and myalgia/arthralgia (75.3%).
* The most reported overall hematological toxicities, included neutropenia (73.3%), leukopenia (69.9%), and anemia (34.9%).
* Patients who received AC regimen suffered more from grade 2 and above leukopenia (35.2% vs. 17.3%, P=0.014), anemia (16.9% vs. 2.7%, P=0.004), and alkaline phosphatase increment (11.3% vs. 2.7%, P=0.039) than AC-T regimen.
* Patients received AC-T regimen suffered more from severe arthralgia/myalgia (2.8% vs. 2%, P=0.001), peripheral neuropathy (1.4% vs. 36%, P=0.000), and gastritis (14.1% vs. 29.3%, P=0.026) than AC regimen
* Predictors of grade two to above hematological toxicities, included pretreatment blood cell counts, having stage IV breast tumor, older age, and lower body surface area.
* Predictors of grade 2 to above oral mucositis, peripheral neuropathy, and fatigue were older age, arthralgia/myalgia, and skin hyperpigmentation, respectively.
* There was high incidences of AC and AC-T regimens-induced toxicities in Ethiopian women with breast cancer.
* Patients who received the AC regimen suffered more from hematological abnormalities, while those on the AC-T regimen experienced more of non-hematological toxicities.

**Harris et al 2018 [29]**

- Pediatric and adolescent population; age 1-18 years
- Hematopoietic cell transplant patients
- Two groups;
* Patients received BuCy=1400
* Patients received BuFlu=381

| Transplant toxicities and outcomes | *Mortality rate
*Transplant toxicities
*Outcomes of each regimen |
|-----------------------------------|--------------------------------------------------|
| * Overall mortality was comparable for children with nonmalignant conditions who received BuFlu or BuCy
* Children transplanted for malignancies were more likely to receive BuFlu; however, there were no differences in transplant toxicities and comparable transplant-related mortality, relapse and treatment failure
* Lower incidences of sinusoidal obstruction syndrome (P ≤ 0.04), hemorrhagic cystitis (P ≤ 0.04), and chronic graft-versus-host disease (P ≤ 0.02) were observed after BuFlu
* Outcomes after BuFlu are similar to those for BuCy for children, but for unclear reasons, those receiving BuFlu for
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Details</th>
<th>Toxicity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yilmaz et al 2015 [30]</td>
<td>Adult patients treated with CYC, patients with severe manifestations of rheumatologic disease, one group=1018 patients</td>
<td>Urotoxicity</td>
<td>* Hemorrhagic cystitis (1.67%), bladder cancer (0.19%) * There were (57.2%) patients who received mesna with intravenous CYC therapy. * There was similar incidence rate for hemorrhagic cystitis in both patient groups concomitantly treated with or without mesna. * There was no proof for the uroprotective effect of mesna. * Cumulative CYC dose (HR for 10-g increments 1.24, p &lt; 0.001) was associated with hemorrhagic cystitis. * Cumulative dose was the only risk factor for hemorrhagic cystitis in patients treated with CYC.</td>
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<tr>
<td>Goekkurt et al 2007 [31]</td>
<td>Adult population (16-59 years) treated with BuCy, HSCT Patients, one group= 84 patients</td>
<td>Liver toxicity</td>
<td>*SOS (43%), relapse (6%), death rate (33%) * MTHFR-A1298C polymorphism as an independent predictor for maximum levels of bilirubin (p=0.0025) and duration of hyperbilirubinaemia (p=0.013) * There was an association between this polymorphism and the occurrence of the SOS (p=0.048) * No significant associations between the MTHFR-C677T or the various GST polymorphisms and liver toxicity were observed. * The MTHFR-A1298C polymorphism might be associated with liver toxicity in patients receiving allogeneic HSCT.</td>
</tr>
</tbody>
</table>

HSCT; hematopoietic stem cell transplantation, PT-Cy; post-transplant cyclophosphamide, ECE; early cardiac events, 4OH-CTX; 4-hydroxy-cyclophosphamide, AC; doxorubicin-cyclophosphamide, AC-T; doxorubicin-cyclophosphamide- followed by paclitaxel, BuCy; busulfan combined with cyclophosphamide, BuFlu; substituting fludarabine for cyclophosphamide, CYC; cyclophosphamide, SOS; sinusoidal obstruction syndrome, GST; glutathione-S-transferase.

There was one study published in 2021 [26], two studies published in 2020 [27, 28], one study published in 2018 [29], one study published in 2015 [30], and the last study was published in 2007 [31]. The studies were conducted either on the adult population [26, 28, 30, 31] or the pediatric population [27, 29]. Three studies were conducted on
hematopoietic stem cell transplant (HSCT) patients [26, 29, 31], one study conducted on a brain tumor in the pediatric population [27], one study involved breast cancer women [28], and the last study was conducted on patients with severe manifestations of the rheumatologic disease [30]. The total number of participants was 3531. There were two studies that included only one group of patients; the study was conducted on patients with severe rheumatologic disease and included 1018 patients [30], and one study was conducted on HSCT patients and included 84 patients [31]. The remaining four studies categorized the patients into two groups. One study was conducted on HSCT divided patients into two groups based on received cyclophosphamide; one group received post-transplant cyclophosphamide (PT-Cy) (136 patients), and the other group involved patients who did not receive PT-Cy (195 patients) [26]. The study conducted on pediatric patients with brain tumors divided patients into two groups based on their age; the first group involved patients with age less than one year (42 patients), the other group involved patients with age of 1-5 years (129 patients) [27]. The third study, which was conducted on breast cancer women, categorized women into two groups based on their medication regimen; one group included patients who received doxorubicin-cyclophosphamide (AC) (71 patients), and the other group included patients who received doxorubicin-cyclophosphamide followed by paclitaxel (AC-T) (75 patients) [28]. The fourth study, which was conducted on the pediatric population who underwent HSCT, divided patients into two groups based on medication regimen; one group received busulfan combined with cyclophosphamide (BuCy) (1400 patients), and the other group received substituting fludarabine for cyclophosphamide (BuFlu) (381 patients) [29].

Different toxicities were investigated by the studies; one study investigated cardiac toxicity and reported the incidence of early cardiac events (ECE), major early cardiac events, and the impact of PT-Cy on cardiac events [26]. Another study reported hematological toxicities and reported the influence of genetic variants on drug exposure and the impact of cyclophosphamide [27]. One study investigated the toxicity profile, including hematological and non-hematological adverse reactions; the study reported these types of toxicities associated with two regimens used (AC regimen and AC-T regimen) and predictors of those toxicities [28]. One study investigated transplant toxicities and outcomes among HSCT patients and reported mortality rate, transplant toxicities, and outcomes of the two regimens used (BuCy,
Urotoxicity was investigated in one study, and the study reported the urotoxicity as well as the protective effect of using Mensa [30]. The last study investigated liver toxicity and reported that toxicity as well as the impact of gene polymorphism on liver toxicity [31].

The results of studies varied from each other as each study had different aims and was conducted on different patients and included different regimens of treatment. The first study reported a cumulated incidence of ECE of 19% among patients who received cyclophosphamide after HSCT; this rate of ECE was higher compared to patients who didn’t receive cyclophosphamide. The major ECEs included ventricular systolic dysfunction (13%), followed by pulmonary edema (7%), then pericarditis (4%). The incidence of ECE was associated with the use of PT-Cy, exposure to cyclophosphamide before HSCT, older age, and sequential conditioning regimen, whereas the cardiovascular risk factors weren’t associated with ECE [26].

The study conducted on breast cancer women showed that the major hematological toxicities included neutropenia (73.3%), leukopenia (69.9%), and anemia (34.9%), whereas the major non-hematological toxicities included fatigue (98.7%), dysgeusia (97.3%), skin hyperpigmentation (96.6%), nausea (93.2%) vomiting (88.4%), gastritis (83.6%) peripheral neuropathy (74%), and myalgia/arthralgia (75.3%). Patients who received the AC regimen significantly experienced grade two and above leukopenia (35.2%), anemia (16.9%), and alkaline phosphatase increment (11.3%) compared to patients who received the AC-T regimen. The predictors of grade two and above hematological toxicity included pretreatment blood cell count, stage IV breast cancer, older age, and lower body surface area. On the other hand, patients who received the AC-T regimen significantly suffered severe arthralgia/myalgia (2.8%), peripheral neuropathy (1.4%), and gastritis (14.1%) compared to patients who received the AC regimen. The predictors of grade two and above non-hematological toxicity included older age [28].

The study conducted on patients with severe manifestations of the rheumatologic disease reported hemorrhagic cystitis of (1.67%) and bladder cancer among (0.19%). The accumulated dose of cyclophosphamide was associated with hemorrhagic cystitis. The incidence of hemorrhagic cystitis wasn’t affected by the administration of mensa [30].
The last study conducted on the adult population to investigate liver toxicity and the impact of gene polymorphism on liver toxicity showed that sinusoidal obstructive syndrome (SOS) was the major toxicity (43%), and the death rate was 33%. MTHFR-A1298C polymorphism was associated with liver toxicity represented by increased levels of bilirubin, and duration of hyperbilirubinemia as well as the occurrence of SOS, whereas MTHFR-C677T or the various glutathione-S-transferase (GST) polymorphism had no association with liver toxicity [31].

The other study conducted on gene polymorphism involved a pediatric population with a brain tumor and treated with 4-hydroxy cyclophosphamide. The higher dose of treatment was related to lower hematological parameters; worse toxicity was associated with higher exposure to the treatment agent. There was no genotype found to affect the drug exposure [27].

The last study was also conducted on the pediatric population administrated two different regimens. The study showed that the two regimens (BuFlu and BuCy) resulted in a comparable rate of mortality. BuFlu regimen was associated with a lower rate of SOS, hemorrhagic cystitis, and chronic graft-versus-host disease [29].

4. Discussion:

Cyclophosphamide is widely used for the treatment of malignancies [32]. Cyclophosphamide is similar to other chemotherapeutic agents and has the risk for teratogenicity, secondary hematologic malignancy, sterility, and both common and opportunistic infections [1]. However, there were few studies that investigated the toxicity of cyclophosphamide, and there was no systematic analysis for such toxicity. Hence, this systematic review was conducted. The first study included in this analysis showed that cyclophosphamide was associated with cardiac toxicity represented by ECE. The role of cyclophosphamide in cardiotoxicity could be evidenced by the finding that cardiovascular risk factors weren't associated with ECE. Moreover, exposure to cyclophosphamide before HSCT was associated with a higher incidence of ECE [26].

A study conducted on 85 breast cancer patients using doxorubicin and cyclophosphamide showed a remarkably higher incidence of grade three and graded four neutropenia as well as a higher incidence of hepatoxicity. The study suggested
ethnic variation affecting the incidence of myelotoxicity among patients [33]. From the previous study, it could be determined that combination therapy of doxorubicin and cyclophosphamide resulted in hepatotoxicity and hematological toxicity represented by neutropenia [33]. In the included studies, it was found that AC regimen (doxorubicin and cyclophosphamide) was associated with grade two and above leukopenia and anemia. AC regimen also was found to be associated with hematological toxicity compared to AC-T patients who received regimen who tended to experience non-hematological toxicities. The study also added more important information and reported the predictors of hematological toxicity associated with AC regimen, including older age, stage of cancer (IV), pretreatment blood cell count, and lower body surface area [28]. Also, the previous study reported that ethnicity might have an impact on myelotoxicity [33], which highlights the involvement of genetic factors in cyclophosphamide-associated toxicity. The genetic impact was investigated in two of six studies; one of the two studies was conducted on the pediatric population [27], and the other study was conducted on the adult population [31]. One study showed that the genotypes had no significant influence on drug exposure, but the toxicity of cyclophosphamide was reduced by reducing the dose [27]. The other study revealed that gene variant of MTHFR-A1298C was associated with hepatotoxicity, whereas other gene variants investigated had no impact [31]. This finding reflects that some gene variants may be involved in increasing the toxicity and highlights the importance of further investigations regarding the genetic impact in patients treated by cyclophosphamide.

One of the studies showed that reducing the dose of cyclophosphamide resulted in a reduction in associated toxicity [27]. Another study revealed that the cumulative dose was the only risk factor for hemorrhagic cystitis among patients treated for cyclophosphamide [30]. This confirms that the dose of cyclophosphamide affects the degree of toxicity the patient experiences, whereas the study investigated the impact of using mensa to reduce the toxicity of cyclophosphamide showed no protective effect of mensa [30].

5. Conclusion:

Cyclophosphamide was associated with various toxicities, including liver toxicity, urotoxicity, cardiac toxicity, hematological and non-hematological toxicities.
toxicity of cyclophosphamide varied based on the regimen and combined medications, as well as some gene variants. However, gene variants require more studies to investigate the gene variants associated with cyclophosphamide-induced toxicities as some gene polymorphisms don’t affect the toxicity. Also, it was found that lowering the dose of cyclophosphamide was effective in reducing the associated toxicities, whereas treatment with mensa didn’t reduce the toxicity. This is the first systematic review and analysis conducted on cyclophosphamide toxicity. There is a need for further studies conducted on this subject as there is a few known about cyclophosphamide-associated toxicity.

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