Post-Transplant Cyclophosphamide for the Prevention of Graft-vs.-Host Disease in Allogeneic Hematopoietic Cell Transplantation: A Guide to Management for the Advanced Practitioner

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Cyclophosphamide remains a critical component to haploidentical transplant conditioning regimens. Post-transplant cyclophosphamide (PTCy) emerged as an effective component of graft-vs.-host disease (GVHD) prophylaxis in the nonmyeloablative haploidentical bone marrow transplant setting. The relative ease of administration compared with ex vivo manipulations and efficacy in reducing GVHD has led to increasing PTCy use in transplant centers around the world. The role of PTCy has expanded to haploidentical transplantation with myeloablative conditioning regimens and peripheral blood progenitor cells as the donor source. Moreover, encouraging results in GVHD management have been shown with the use of PTCy alone or in combination with other immunosuppressives in the human leukocyte antigen–matched donor setting. The toxicity profile of cyclophosphamide varies extensively depending on dose, duration, overall drug exposure, and, potentially, pharmacogenetics. This review highlights the pharmacology, pharmacokinetics, and toxic effects of cyclophosphamide and offers practical guidance for clinical application in the post-transplant setting. We summarize data on the management of high-dose cyclophosphamide toxicities and provide insights into the pharmacogenetic implications on drug efficacy and safety data.

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Since its first US Food and Drug Administration (FDA) approval in 1959, cyclophosphamide use has expanded to solid and hematologic malignancies, autoimmune diseases, and mobilization and conditioning regimens for hematopoietic cell transplantation (HCT). More recently, cyclophosphamide has emerged as an attractive strategy for the prevention of graft-vs.-host disease (GVHD) in the setting of allogeneic hematopoietic cell transplantation (allo-HCT).

Based on data supporting the safety and effectiveness of this method, the use of high-dose post-transplant cyclophosphamide (PTCy) in the haploidentical and human leukocyte antigen (HLA)-matched settings continues to increase. Although no strict definition exists, cyclophosphamide doses of 50 mg/kg and above will be considered high for this review. The toxicity profile of cyclophosphamide varies depending on the dose, duration of use, and overall drug exposure, with high doses associated with more acute toxicities but lower risk of chronic side effects (Emadi et al., 2009). Due to the relative novelty of PTCy compared with high-dose cyclophosphamide (HDCy) in the pretransplant setting, most of the published safety data is based on the latter. The aim of this article is to provide a comprehensive review of cyclophosphamide-associated toxicities, their management, pharmacokinetic and pharmacogenetic factors toward a personalized approach, and methods to improve both the safety and efficacy of this chemotherapeutic strategy.

MECHANISM OF ACTION

Cyclophosphamide is an alkylating agent with an active metabolite, phosphoramide mustard, that prevents cell growth by crosslinking DNA strands. While effective throughout the cell cycle, cells rapidly undergoing mitosis are particularly sensitive to cyclophosphamide due to the reduced ability to replicate the damaged DNA (Emadi et al., 2009). Aldehyde dehydrogenase is responsible for the conversion of phosphoramide mustard to an inactive metabolite. Hematopoietic stem cells rich in this enzyme are resistant to cyclophosphamide, allowing for its use soon after HCT without impairing engraftment (Mayumi et al., 1996). Based on murine model data, regulatory T cells (Tregs) have particularly high expression of aldehyde dehydrogenase and thus are not susceptible to cytotoxic cyclophosphamide effect (Luznik et al., 2010).

A three-step mechanism to explain the stimulation of immuno-tolerance by PTCy has been proposed and is described in Figure 1 (Luznik et al., 2010; Mayumi et al., 1996). Among currently employed post-transplant immunosuppressants, only cyclophosphamide and methotrexate can induce apoptosis of alloantigen-activated human T cells (Strauss et al., 2002). Traditional GVHD prophylaxis agents, such as calcineurin inhibitors and sirolimus, weaken alloreactive T cell activation, proliferation, and interleukin-2 production without causing apoptosis, which may lead to delayed induction of transplant tolerance (Strauss et al., 2002). Another unique cyclophosphamide mode of action is upregulation of CD95 expression, which leads to activation-induced apoptosis within 6 days, further preventing T-cell activation (Strauss et al., 2002).

CYCLOPHOSPHAMIDE IN THE POST-TRANSPLANT SETTING

The use of PTCy was first established in the prevention of graft rejection and GVHD in the setting of haploidentical T cell replete HCT with nonmyeloablative conditioning (Luznik et al., 2008; O'Donnell et al., 2002). Historically, nonmyeloablative haploidentical transplant included low-dose pretransplant cyclophosphamide (typically 14.5 mg/kg/day), nonmyeloablative conditioning with low-dose total body irradiation (TBI), and fludarabine (Luznik et al., 2008; O'Donnell et al., 2002). Graft-vs.-host disease prophylaxis included PTCy, mycophenolate mofetil (MMF), and tacrolimus. These trials established the PTCy dosing regimen of cyclophosphamide 50 mg/kg on days +3 and +4. Some studies, mostly retrospective, support that the incorporation of PTCy does not compromise engraftment or lead to worsened progression-free or overall survival, and can decrease the risk of GVHD (Ciurea et al., 2015; Ghosh et al., 2016; Luznik et al., 2008). Post-transplant cyclophosphamide effectiveness in preventing GVHD in the haploidentical setting led to further investigation and successful use with myeloablative conditioning regimens and peripheral blood stem cells (PBSC) as the graft source (Table 1; Bashey et al., 2016; Castagna et al., 2014; Solomon et al., 2016).

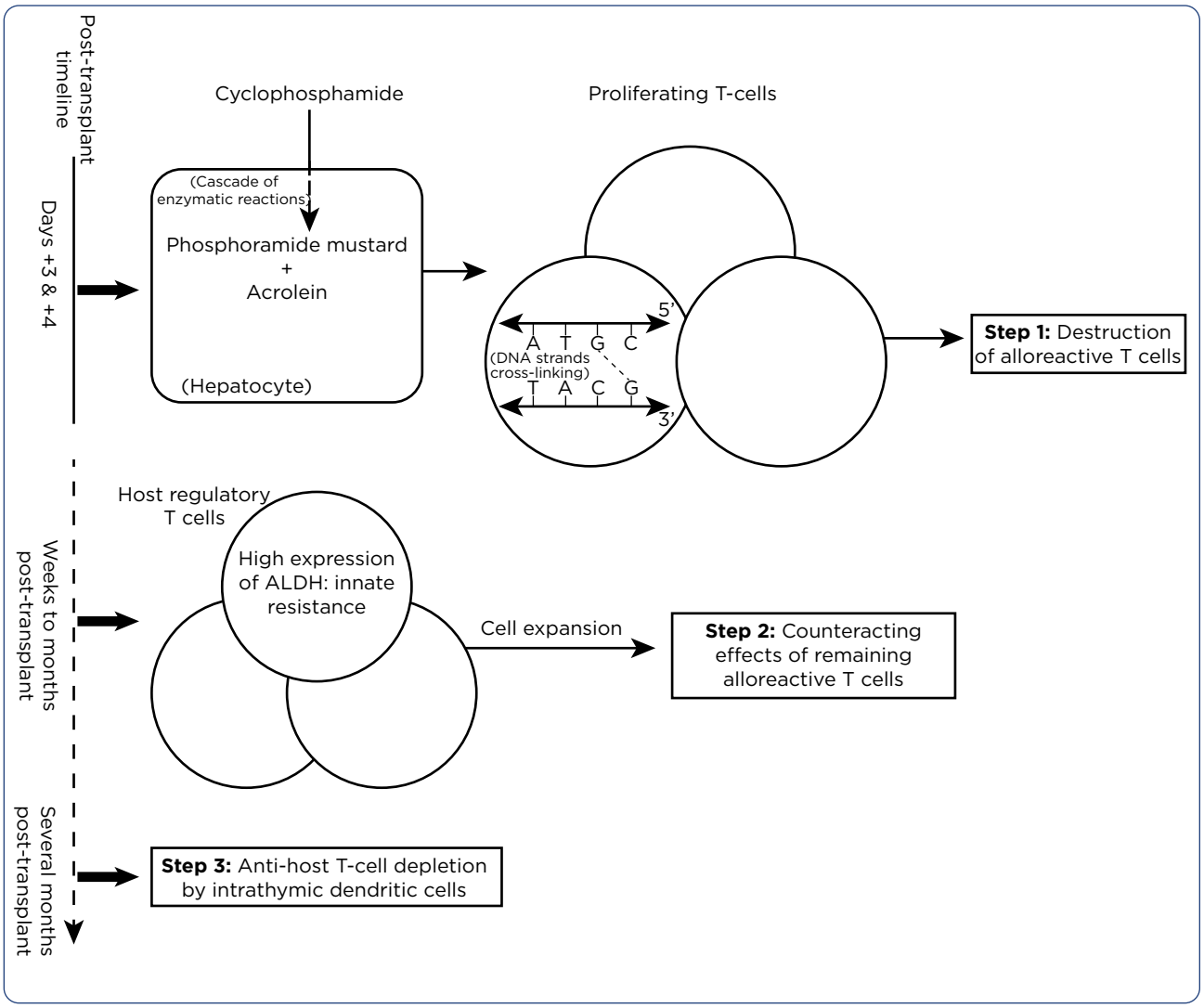

Figure 1. A three-step mechanism of immuno-tolerance by post-transplant cyclophosphamide (PTCy). Step one involves selective destruction of rapidly proliferating alloreactive donor and recipient T cells after administration of PTCy. The second step occurs during the next several weeks or months following transplant. Host regulatory T cells expand and counteract the effect of remaining alloreactive mechanisms. In the final step, anti-host T cells are deleted by intrathymic dendritic cells. This step maintains long-term tolerance; however, it generally takes several months for development. ALDH = aldehyde dehydrogenase.

The role of PTCy alone or in combination with other immunosuppressants has been investigated in the HLA-matched setting with encouraging results. Among 92 patients diagnosed with acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS) and treated with PTCy as the sole GVHD prophylaxis after myeloablative HLA-matched HCT, low chronic GVHD rates and similar relapse and survival rates when compared with other GVHD prophylaxis approaches were reported (Kanakry et al., 2014). Alternatively, high rates of severe acute GVHD led to the closure of a study by Bradstock and colleagues (2015), suggesting PTCy as the sole GVHD prophylaxis may be inadequate with PBSC grafts after reduced intensity conditioning in the HLA-matched setting (Holtick et al., 2016). Holtick and colleagues (2016) reported high rates of severe acute GVHD and nonrelapse mortality after utilizing HLA-matched PBSC and PTCy as the sole GVHD prophylaxis. Multiple authors reported overall and event-free survival outcomes similar to those from the bone marrow cell source.

Table 1. Considerations for the Administration of Post-Transplant Cyclophosphamide

Patient Counseling Points
- Hemorrhagic cystitis
- Cardiotoxicity (acute decompensated heart failure; long term heart failure/myopathy)
- Infectious risks (utilize prophylactic measures)
- Secondary leukemia/malignancies
- Nausea/vomiting
- Infertility/gonadal dysfunction

Advantages of Administration
- Effective GVHD reduction as compared with standard prophylactic therapies (10%–30%)
- Relatively easy handling/administration (short infusion time, lack of infusion-related reactions)
- Reduced incidence of mucositis and hepatoxicity with PTCy-tacrolimus-mycophenolate compared with methotrexate-tacrolimus prophylaxis
- Cost effective

Disadvantages of Administration
- Despite nonmyeloablative/reduced intensity preparative regimens, the incorporation of PTCy may be too toxic for select patients (e.g., elderly, multiple comorbidities)
- Increased risk of secondary malignancies, especially in the setting of cure and long-term expected survival

Note. GVHD = graft-vs.-host disease; PTCy = post-transplant cyclophosphamide.

To improve outcomes, PTCy has been evaluated in combination with additional GVHD prophylaxis agents. Moiseev and colleagues (2016) conducted a single-center trial combining PTCy, tacrolimus, and MMF as GVHD prophylaxis for 86 unrelated PBSC transplant patients. The authors reported superior acute and chronic GVHD control, survival, and safety of this approach compared with historical control with antithymocyte globulin (ATG)-based prophylaxis (Moiseev et al., 2016). Post-transplant cyclophosphamide (PTCy) has also been successfully combined with cyclosporine, yielding low rates of chronic GVHD without significant impact on control of the underlying malignancy (Mielcarek et al., 2016). In 2018, Ruggeri and colleagues reported that the addition of two immunosuppressive agents (cyclosporine and methotrexate or cyclosporine and MMF) to PTCy was associated with reduced rates of chronic GVHD and improved survival compared with PTCy alone among 423 acute leukemia patients receiving HLA-matched transplantation.

PHARMACOLOGIC CONSIDERATIONS FOR DOSING PTCy

Pharmacokinetics

Cyclophosphamide is a prodrug extensively metabolized in the liver (Figure 2). Approximately 15% of the administered dose is excreted unchanged by the kidneys and 5% in bile (Boddy & Yule, 2000). A notable difference in the mean half-life and total body clearance of cyclophosphamide is seen between patients with and without liver impairment (Juma, 1984). The package insert does not provide any dosing recommendations for patients with impaired hepatic function. Floyd and colleagues (2006) suggested a 25% reduction in the cyclophosphamide dose for patients with a serum bilirubin of 3 to 5 mg/dL or transaminases at least three-fold above the upper limit of normal (ULN), a notable consideration when administering high doses. Some data suggest the half-lives of cyclophosphamide and its active metabolite are significantly longer in patients with renal impairment, however, cyclophosphamide dose adjustment is not necessary unless kidney impairment is severe (Haubitz et al., 2002; Juma et al., 1981).

Obesity can alter the pharmacokinetics of chemotherapies due to decreased blood flow to the liver and kidneys, increased drug protein binding, relative shift of lipophilic drugs to adipose tissue, and impaired hepatic clearance (Navarro, 2003). These factors suggest that using total body weight (TBW) for dosing cyclophosphamide in patients with obesity may result in drug overexposure, leading to higher rates of toxicities including hemorrhagic cystitis (HC), cardiac toxicities, and sinusoidal obstructive syndrome. Without translating into differences in safety or efficacy, a two-fold increase in the area under the curve (AUC) of the active metabolite 4-hydroxycyclophosphamide (HCY) was reported in obese patients compared with nonobese patients (De Jonge et al., 2002). Hunter and colleagues (2016) reported a study utilizing adjusted body weight (ABW) comparing the differences in cyclophosphamide response between obese (n = 28) and nonobese (n = 33) allo-HCT

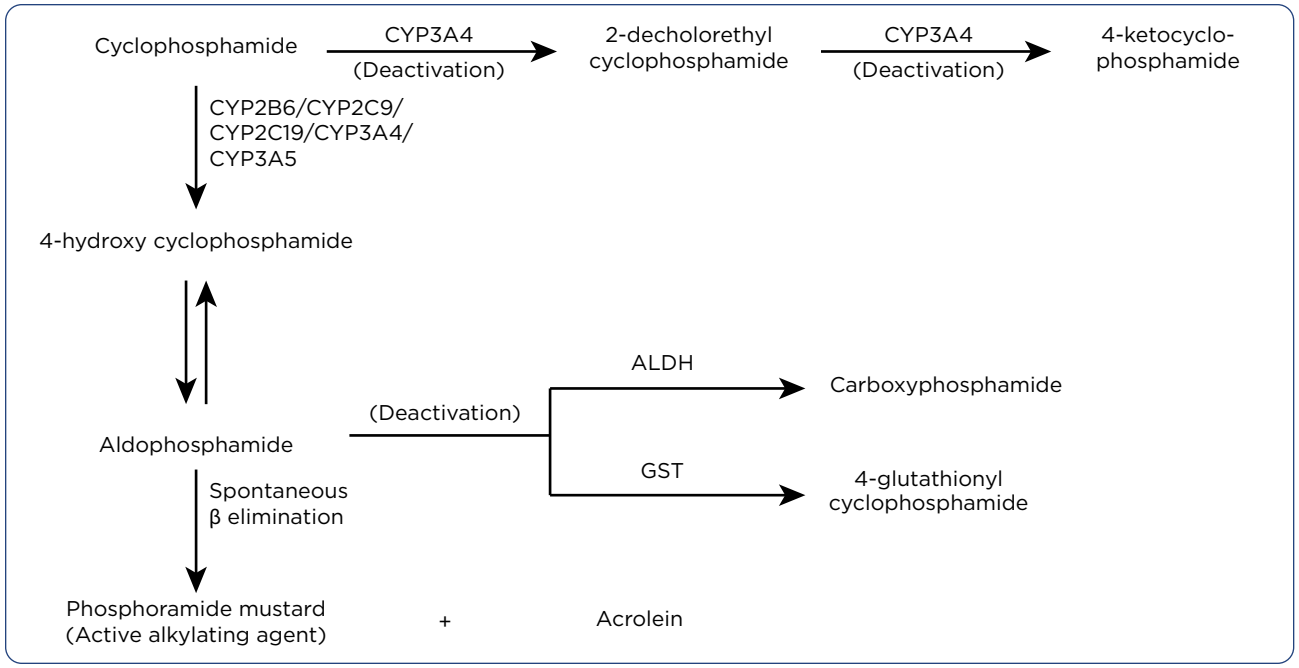

Figure 2. Cyclophosphamide metabolic pathway. Cyclophosphamide activation is mediated by the cytochrome P450 isoenzymes, and involves its conversion to 4-hydroxy cyclophosphamide. This metabolite partially tautomerizes into aldophosphamide, which undergoes non-enzymatic degradation into phosphoramide and acrolein. Phosphoramide is responsible for DNA cross-linking (cytotoxicity), acrolein for bladder toxicity. Both are detoxified or inactivated by glutathione transferase. Alternatively, aldophosphamide may be oxidized by aldehyde dehydrogenase to inactive carboxyphosphamide.
ALDH = aldehyde dehydrogenase; GST = glutathione transferase.

recipients. Relapse rates at day +100 did not differ significantly between the two groups. Despite this, the overall rate of renal dysfunction was significantly higher in obese patients compared with nonobese patients, which was primarily attributed to the higher prevalence of diabetes among obese patients. A study of obese patients with lymphoma who received HDCy conditioning followed by autologous HCT yielded no significant differences in post-transplant complications, relapse rates, or survival between normal weight, overweight, and obese patients (Lau et al., 2015).

From these studies, we can deduce that obese patients receiving dose-adjusted cyclophosphamide in preparation for HCT have comparable outcomes to nonobese patients. It is important to note, however, that doses evaluated in the reported trials are often higher than the PTCy dose. To our knowledge, there are no studies evaluating the effect of obesity and the chosen dosing weight in the PTCy setting. The American Society for Blood and Marrow Transplantation (ASBMT) guidelines recommend using the lesser of TBW or ideal body weight (IBW) for patients receiving cyclophosphamide at a total dose of 200 mg/kg. For adult patients receiving a total dose of 120 mg/kg, IBW or ABW can be used (Bubalo et al., 2014). Of note, these recommendations are based on expert opinions. Due to the current knowledge gap of how to optimally dose PTCy in obese patients, it is pivotal that centers using this strategy to prevent GVHD follow the recommendations set forth by ASBMT.

Pharmacogenetics

Pharmacogenetic variations in drug metabolism genes, including *CYP2B6*, *CYP2C19*, *CYP3A4*, and *CYP3A5*, may influence exposure to the parent drug and its active metabolite, HCY (Boddy & Yule, 2000). Based on the pharmacology of cyclophosphamide, increased formation of HCY would be expected to both increase treatment efficacy and risk of toxicity whereas reduced formation of HCY may reduce clinical response. Pharmacogenetic variations in genes involved with the detoxification of HCY, including *ALDH* and *GST*, may also influence HCY exposure and drug response.

To date, there is only one published study in the PTCy setting. An abstract by Patel and colleagues (2018) investigated the association between polymorphisms in *ALDH1A1*, *ALDH3A1*, *GSTA1*, *GSTM1*, *GSTP1*, *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP3A4* and *CYP3A5*, and clinical outcomes in 59 allo-HCT patients receiving fludarabine, cyclophosphamide, TBI, and PTCy. Results demonstrated improved overall survival in *ALDH3A1* intermediate vs. poor metabolizers (hazard ratio [HR] 0.22; 95% confidence interval [CI] = 0.06–0.82; p = .02), *CYP3A5* poor vs. normal metabolizers (HR 0.18; 95% CI = 0.04–0.83), and *CYP3A4* normal vs. intermediate metabolizers (HR 0.17; 95% CI = 0.05–0.63; p = .008). A similar improvement in progression-free survival was noted for *CYP3A4* normal vs. intermediate metabolizers (HR 0.14; 95% CI = 0.04–0.45; p = .001). *GSTP1* normal metabolizers had a lower risk of cardiotoxicity compared with poor metabolizers (odds ratio [OR] 0.09; 95% CI = 0.01–0.45; p = .007), and *ALDH1A1* normal metabolizers had a lower risk of HC compared with intermediate metabolizers (OR 0.09; 95% CI = 0.004–0.65; p = .036). Given the limited sample size and lack of replication studies in the PTCy setting, larger prospective studies are needed to validate these findings.

Additional studies focused on the identification of candidate genes in patients with various hematologic malignancies receiving cyclophosphamide as treatment or conditioning. A study of allo-HCT recipients conditioned with busulfan and cyclophosphamide demonstrated that carriers of *CYP2B6*2A* or *CYP2B6*4* had an increased risk of HC and oral mucositis through increased activation of the prodrug (Rocha et al., 2009). In a study of 455 chronic lymphocytic leukemia patients receiving fludarabine and cyclophosphamide, investigators identified that patients carrying at least one *CYP2B6*6* allele resulted in reduced enzyme activity and were less likely to achieve a complete response (OR 0.27; p = .004; Johnson et al., 2013). Multivariate analysis controlling for age, gender, stage, mutational status, 11q deletion, and *TP53* deletion/mutation identified *CYP2B6*6* and *TP53* mutation/deletion as the only independent determinants of achieving a complete response. Another study explored the relationship between cyclophosphamide pharmacokinetics and polymorphisms in *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP3A5*, and *GSTA1* (Timm et al., 2005). Results demonstrated that *CYP2C19*2* was significantly associated with cyclophosphamide exposure at doses ≤ 1,000 mg/m^2; however, no correlation was made to clinical response.

Studies have also investigated genes involved in the detoxification of cyclophosphamide metabolites. In 90 adult Hodgkin lymphoma patients treated with cyclophosphamide, those with at least one *GST* deletion (*GSTM1* or *GSTT1*) had significantly better disease-free survival (p = .012; Hohaus et al., 2003). Rossi and colleagues (2009) demonstrated that patients with B-cell lymphoma carrying the heterozygous or homozygous variant genotype for *GSTA1* rs3957357 (CT/TT) had significantly improved event-free survival compared with wild-type patients (HR 0.38, p = .003; Rossi et al., 2009). Similarly, a study of Hodgkin lymphoma patients treated with cyclophosphamide identified that the *GSTP1* Ile(105)Val polymorphism was an independent prognostic factor for survival. The probability of 5-year survival for patients homozygous for the (105)Val/(105)Val *GSTP1* genotype was 100%, for heterozygous patients 74%, and for homozygous patients 43% (Hohaus et al., 2005). Other studies in multiple myeloma and childhood ALL have shown similar results, whereby polymorphisms in GST are noted to improve treatment outcomes after cyclophosphamide (Dasgupta et al., 2003; Stanulla et al., 2000). These data suggest that reduced inactivation of cyclophosphamide metabolites may increase cytotoxicity, thus enhancing clinical efficacy but also potentially increasing the risk of adverse events.

Given the functionality of these genes, it is hypothesized that prior findings may translate to the PTCy setting; however, given the paucity of data in the PTCy setting, the current level of evidence is insufficient to warrant preemptive pharmacogenetic testing to individualize PTCy dosing in clinical practice and necessitates prospective validation.

TOXICITY AND MANAGEMENT CONSIDERATIONS FOR THE ADVANCED PRACTITIONER

Cardiotoxicity

Cyclophosphamide-induced cardiotoxicity (CIC) is a dose-limiting toxicity reported after administration of high doses. While the exact mechanism of CIC has not been elucidated, it is not related to cumulative exposure (Morandi et al., 2005).

Cyclophosphamide-induced cardiotoxicity may involve oxidative stress and direct endothelial capillary injury resulting in extravasation of toxic metabolites, direct damage to cardiomyocytes, interstitial hemorrhage, edema, and microthrombi.

The clinical manifestations of CIC range widely and include subclinical depression of left ventricular function, arrhythmias, pericardial effusions, heart failure, myocarditis, and, most fatally, hemorrhagic necrotic perimyocarditis (Table 2; Morandi et al., 2005). Acute symptom onset typically occurs during or within 3 weeks of HDCy administration and may resolve without any late sequelae. The reported incidence of HDCy-induced acute heart failure ranges from 7% to 43% (Morandi et al., 2005). In the HCT setting, up to 45% of transplant recipients reported temporary CIC with HDCy conditioning; the incidence of fatal cardiotoxicity was reported at around 1.5% (Ishida et al., 2016).

Data on CIC with PTCy specifically is scarce. A small retrospective report suggests that the risk of cardiotoxicity might be increased with PTCy (Souchet et al., 2013). In this report, 3 out of 11 evaluated patients who received PTCy developed a compressive pericardial effusion, with 1 patient expiring secondary to refractory cardiogenic shock on day +16. No infectious etiology was identified in these cases, and all patients had normal cardiac function with no known cardiovascular risk factors prior to transplant. The rate of early cardiac-related death was higher with PTCy compared with institutional rates in transplants without PTCy. A larger retrospective analysis reports a 21.9% incidence of post-transplant cardiomyopathy and 13.6% incidence of pericardial effusion among 160 patients who received PTCy (Lin et al., 2017). Sixty percent of patients with cardiomyopathy died within a month of the event. Among 14 survivors, cardiomyopathy resolved in 64% of cases. Based on

Table 2. Management of Most Common Treatment-Related Complications Associated With PTCy

Complication	Manifestations	Management
Cardiotoxicity	Cardiac arrhythmias, pericardial effusions, heart failure, cardiac tamponade, hemorrhagic myocarditis	• Monitor vital signs, signs of fluid retention, daily weights. Consider labs (BNP, troponin), EKG (QT dispersion, QTc), echo (if CIC suspected) • Management is similar to treatment considerations for general population approach for developed cardiac condition • Cardiac tamponade and hemorrhagic myocarditis require aggressive care and early involvement of intensive care should be considered • The optimal management of hemorrhagic myocarditis is unknown due to almost uniform fatality
Hemorrhagic cystitis	Blood in the urine, pain in the bladder, bladder spasms, thrombocytopenia	• Preventative measures including hyperhydration, forced diuresis, frequent voiding, and the use of mesna should be employed • Monitor the patient for fluid overload, congestive heart failure, and electrolyte imbalances • Supportive care is the mainstay of treatment for hemorrhagic cystitis. Patients should receive hyperhydration, antispasmodics, pain management, and platelet transfusions as needed
Electrolyte abnormalities	Water intoxication similar to SIADH, with dilutional hyponatremia and euvolemic fluid balance	• Hyponatremia typically lasts 20–24 hours, correlating with urinary excretion of cyclophosphamide metabolites • Symptoms may include fatigue, weakness, headache, nausea, vomiting, diarrhea, somnolence, and progress to confusion, psychosis, convulsions if hyponatremia becomes severe • Diuresis to promote a euvolemic state prior to administering PTCy is recommended to prevent fluid overload • Isotonic saline is the preferred concomitant fluid during PTCy administration • Close monitoring and reduction in IV fluid rate the day after cyclophosphamide administration are recommended to help with fluid balance

Note. EKG = electrocardiography; BNP = brain natriuretic peptide; echo = echocardiogram; CIC = cyclophosphamide-induced cardiotoxicity, PTCy = post-transplant cyclophosphamide; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

multivariate analysis, age greater than 60 years and hematopoietic cell transplantation-specific comorbidity index (HCT-CI) equal to or greater than 4 were statistically significant risk factors for cardiomyopathy. Compared with a matched cohort of patients not receiving PTCy, the incidence of post-transplant cardiomyopathy among PTCy recipients was not significantly higher (15% and 22%, respectively).

In general, the total dose of cyclophosphamide is an accepted risk factor for CIC (Ishida et al., 2016). Although the minimal threshold dose has not been established, there are no reports of CIC at doses less than 100 mg/kg. Reported risk factors include older age, prior radiation to the mediastinum or left chest wall, preexisting left ventricular dysfunction, preexisting risk factors for ischemic cardiac disease, and exposure to other cardiotoxins (Dhesi et al., 2013). A prior cumulative dose of doxorubicin less than 450 mg/m^2 does not appear to confer an increased risk for CIC.

There are no established guidelines for the prevention or management of CIC. Given the risk for severe and even fatal cardiotoxicity, vigilant monitoring and early detection of CIC are critical. Common nonspecific electrocardiogram (EKG) alterations include low QRS voltage and T-wave or ST-segment abnormalities (Dhesi et al., 2013). Prolonged corrected QT (QTc) and increased QTc dispersion have been reported as early findings of cyclophosphamide-induced acute heart failure (Nakamae et al., 2004). On echocardiography, change in E/A ratio (ratio of peak velocity of early filling [E] to mitral peak velocity of late filling [A]), intraventricular septum thickness in diastole, increased left ventricular diastolic/systolic diameter, and early functional mitral regurgitation are early findings associated with CIC (Ishida et al., 2016; Morandi et al., 2001; Nakamae et al., 2004). Based on several reports, early CIC is characterized by diastolic rather than systolic dysfunction (Ishida et al., 2016; Morandi et al., 2001). Findings associated with hemorrhagic myocarditis may include hypertrophy, decreased left ventricular ejection fraction, and elevated myocardial echogenicity (Birchall et al., 2000; Ishida et al., 2016). B-type natriuretic peptide and troponin I or T are circulating cardiac markers that may be valuable in the monitoring of CIC. Morandi and colleagues (2001) reported that peak troponin levels between days 8 and 15 post HDCy administration are suggestive of direct myocardial damage.

If EKG abnormalities are identified, fluid and electrolyte optimization and close vitals monitoring during and after cyclophosphamide administration should be recommended. Pericardial effusions can be managed with glucocorticosteroids and analgesics, and generally resolve without serious complications. Heart failure should be treated according to the American College of Cardiology/American Heart Association guidelines and is generally reversible with appropriate management (Dhesi et al., 2013; Yancy et al., 2017). Timely and aggressive diuretics should be employed to maintain fluid balance, especially during the administration of high volumes of intravenous fluids. Additionally, angiotensin-converting enzyme inhibitors and β-blockers should be instituted early if there are no contraindications. If cardiac tamponade, hemorrhagic myocarditis, or cardiogenic shock are suspected, prompt involvement of intensive care should be strongly considered (Dhesi et al., 2013; Ishida et al., 2016). To prevent hypoperfusion-related morbidity and mortality, extracorporeal membrane oxygenation and mechanical circulatory support may be considered. Due to the rarity and almost uniform fatality of hemorrhagic myocarditis, the optimal therapeutic approach remains unknown. There are a few reports of theophylline and ascorbic acid therapy in cases of severe CIC (Lee et al., 1996), however, the evidence for these therapies is limited.

Hemorrhagic Cystitis

Hemorrhagic cystitis is reported in 10% to 70% of patients receiving HDCy (Gonella et al., 2015; Ruggeri et al., 2015; Seber et al., 1999). This risk is increased to 31% to 75% in haploidentical HCT patients (Ruggeri et al., 2015). The large range in incidence may reflect a lack of consistency across HC definitions and severity scales. Hemorrhagic cystitis can contribute to morbidity, delay hospital discharge, and increase the rate of readmission.

Hemorrhagic cystitis that occurs soon after the administration of cyclophosphamide is thought to be related to drug exposure, whereas late-onset HC is often attributed to a variety of factors including viral infections (BK virus, cytomegalovirus, adenovirus), intensity of conditioning regimen, thrombocytopenia, GVHD, and donor type (Gonella et al.,

2015; Ruggeri et al., 2015; Seber et al., 1999). A few studies conducted in the PTCy setting discuss the incidence of HC; however, these cases are related to BK virus (Shah et al., 2019; Solomon et al., 2014). The definition of early-onset HC is difficult to describe as it varies significantly from study to study. Some studies designate early as within 24 hours of administration of cyclophosphamide and others up to 21 days after administration (Gonella et al., 2015).

While the time frame of early onset HC is not well defined, the etiology is understood. Early onset HC involves damage to the bladder wall. Acrolein is the cyclophosphamide metabolite that is attributed to urothelial toxicity (Seber et al., 1999). Acrolein increases the production of reactive oxygen species in the bladder, which can cause edema, inflammation, ulceration, hemorrhage, and necrosis of the urothelium within a few hours. This is further augmented by extended exposure of the bladder epithelium to acrolein and urinary route of excretion.

Currently no randomized controlled trials have been conducted to support the use of one method of HC prevention over another. Ultimately, the goal is to decrease the concentration of acrolein and time that it is in contact with the bladder epithelium. This may be accomplished with hyperhydration, forced diuresis, frequent voiding, and the use of mesna (sodium 2-mercaptoethanesulfonate; Gonella et al., 2015; Ruggeri et al., 2015; Seber et al., 1999). In particular, mesna contests HC by binding acrolein, forming an inert compound than can pass through the urine, thus preventing it from harming the bladder urothelium. Mesna is not active outside of the urinary tract; therefore, it can be simultaneously administered with cyclophosphamide without diminishing the cytotoxic effect. Prophylaxis with fluoroquinolones, urethral catheterization, and continuous bladder irrigation have been trialed but have not demonstrated success (Gonella et al., 2015). Adverse effects associated with HC prevention may include fluid overload, congestive heart failure, and electrolyte imbalances with hyperhydration; patient discomfort; and increased incidence of microscopic hematuria with continuous bladder irrigation (Seber et al., 1999). Our institution has been administering normal saline at a rate of 3 mL/kg/hour based on ABW up to a maximum rate of 250 mL/hour on days of PTCy. Based on observation, this approach is effective in HC prevention and well tolerated. Formal studies evaluating this intervention have not been conducted.

Once the patient has been diagnosed with HC, the mainstay of treatment is supportive care with hyperhydration, antispasmodics, pain management, and platelet transfusions as needed (Ruggeri et al., 2015). Intravenous immunoglobulin administration can be considered if the HC is related to a viral infection. Serious cases may require continuous bladder irrigation, cystoscopy to remove clots, percutaneous nephrostomy placement for persistent hydronephrosis, or installation of topical therapies (prostaglandins, alum, formalin, aminocaproic acid, glutamine). Despite limited available data, other options include hyperbaric oxygen therapy, fluoroquinolone antibiotics, and the application of fibrin glue (Ruggeri et al., 2015). Similar to preventative measures, there is no consensus on preferred treatment modality. The authors would recommend hyperhydration, antispasmodics, pain management, and platelet transfusions to support patients with HC.

Electrolyte Abnormalities

High doses of cyclophosphamide have been linked to water intoxication and death (DeFronzo et al., 1974; Steele et al., 1973). The mechanism behind cyclophosphamide-induced water intoxication is unknown but appears to be related to an antidiuretic hormone (ADH)-like mechanism. Cyclophosphamide or its metabolites may have a direct effect on the kidney, causing enhanced permeability of the distal tubules to water (Steele et al., 1973). Water intoxication presents similarly to syndrome of inappropriate antidiuretic hormone secretion (SIADH) with dilutional hyponatremia and a relatively euvolemic fluid balance (DeFronzo et al., 1974). Unlike SIADH, vasopressin administration had no effect on urine flow and free water excretion when studied in this population.

No correlation has been demonstrated between cyclophosphamide-induced water intoxication and nausea/vomiting, changes in glomerular filtration rate, urine sodium excretion, or electrolyte derangements other than sodium (DeFronzo et al., 1974; Steele et al., 1973). Cyclophosphamide-associated hyponatremia typically involves decreased serum osmolarity and increased urine osmolarity within 4 to 12 hours of cyclophosphamide administration.

Urine flow and free water excretion are decreased and hyponatremia ensues. These derangements last 20 to 24 hours, which is theorized to correlate with urinary excretion of cyclophosphamide alkylating metabolites (DeFronzo et al., 1974; Steele et al., 1973).

When symptoms occur, they are characteristic of hyponatremia. Mild symptoms include fatigue, weakness, headache, nausea, vomiting, diarrhea, somnolence, and may progress to lethargy, confusion, psychosis, convulsions and even coma or death in severe cases (Sorensen et al., 1995). Syndrome of inappropriate antidiuretic hormone secretion is normally treated with fluid restriction; however, due to the risk of HC, this is not an optimal treatment modality in patients receiving PTCy. DeFronzo and colleagues (1974) suggest that patients receiving HDCy should receive hydration prior to therapy, receive a slow rate continuous infusion of IV fluids over 24 hours while the cyclophosphamide is being administered, decrease the rate of IV fluids if weight gain is observed, and avoid the use of diuretics since the hyponatremia is usually self-limiting within 24 hours. Alternatively, some experts argue that fluid restriction may be employed if the patient is closely monitored and concomitantly administered isotonic normal saline with diuretics and electrolyte replacement (Sorensen et al., 1995). To alleviate electrolyte abnormalities, we recommend patients undergo diuresis to obtain a euvolemic fluid status prior to PTCy to prevent fluid overload. Isotonic saline is our preferred concomitant fluid during PTCy administration. Patients should be closely monitored after cyclophosphamide administration, and the IV fluid rate should be decreased the day after cyclophosphamide administration to help with fluid balance.

Other Toxicities

The most commonly reported toxicities secondary to cyclophosphamide administration are nausea, vomiting, alopecia, immunosuppression, and gonadal damage. These toxicities reflect cyclophosphamide's effect on rapidly proliferating cells such as hematopoietic cells, epithelial cells of the gastrointestinal tract, hair follicles, and gonads (Emadi et al., 2009). Although not specifically reported in the setting of PTCy, clinicians may consider these toxicities notably higher than standard chemotherapy regimens. It should be noted that other chemotherapeutics administered prior to PTCy (e.g., the conditioning regimen) may be associated with these toxicities as well.

Nausea and vomiting prophylaxis with 5-hydroxytryptamine 3 (5-HT3) receptor antagonists, such as ondansetron or granisetron, can usually mitigate these adverse effects. Few studies have evaluated the most effective antiemetic prophylaxis during high-dose and multiday chemotherapy, particularly during PTCy. In recent guidelines, Hesketh and colleagues (2017) recommended a three-drug combination of a neurokinin 1 (NK1) receptor antagonist, 5-HT3 receptor antagonist, and dexamethasone. Unlike the preparative setting, the use of steroids should be discouraged in the post-transplant/pre-engraftment setting where PTCy is administered to optimally preserve the stem cell graft. Clinicians should consider the use of scheduled NK1 antagonists and 5-HT3 antagonists, with consideration for on-demand dopamine antagonists before, during, and for 2 to 3 days following the administration of PTCy. Additionally, diarrhea may occur following high-dose therapy. After screening for infection, diarrhea should be treated symptomatically in accordance with institutional standards (Emadi et al., 2009).

The use of TBI, cyclophosphamide, and busulfan as a part of conditioning regimens has been associated with sinusoidal obstruction syndrome (SOS) or veno-occlusive disease (VOD; Dalle & Giralt, 2016). A concern with the increased use of PTCy may be the increased potential for VOD. Despite this heightened concern, results have not yet confirmed this finding to date. Moiseev and colleagues (2016) compared GVHD prophylaxis with PTCy in 86 patients to an antithymocyte globulin-based regimen in 125 historical controls undergoing an unrelated HCT. Results showed a significantly reduced incidence of VOD with PTCy with improved tolerability (Moiseev et al., 2016).

Ovarian failure is another potential complication of HDCy administration, with increased risk among those of older age, higher cumulative doses, and more frequent administration (Sanders et al., 1988). While sperm storage prior to chemotherapy is a widely practiced and technically successful modality, the functionality of egg, embryo, and ovarian preservation remains uncertain for women seeking to preserve their reproductive potential.

Chemotherapy received in preparation for transplant (including PTCy) may impact gonadal function. Patients should receive appropriate counseling regarding the impact of chemotherapy on fertility followed by a referral to fertility counseling services.

CONCLUSION

Post-transplant cyclophosphamide has significantly changed the field of allogeneic stem cell transplantation with growing interest as GVHD prophylaxis in the haploidentical and HLA-matched settings. The toxicity profile of cyclophosphamide varies extensively depending on the dose and duration of use, with high doses associated with increased acute toxicities. Clinicians should be familiar with potential side effects of PTCy and to provide optimal patient care. An understanding of the pharmacokinetic pathways of cyclophosphamide metabolism is imperative to avoid drug interactions. This and a knowledge of the impact of genetic differences on toxicity or efficacy may offer the possibility of personalized dosing.

It is likely that a "one size fits all" approach with PTCy dosing in T-cell replete haploidentical HCT is suboptimal. An understanding of the influence of donor and recipient pharmacogenetics, drug pharmacokinetics, and T-cell phenotypes will permit a tailored dosing strategy to improve the therapeutic index of PTCy and optimize the graft vs. tumor effect, while minimizing acute and chronic GVHD.

In order to develop clinical tools predictive of cyclophosphamide response, our group is performing a study to examine both donor and recipient pharmacogenetics, cyclophosphamide (and related metabolites) pharmacokinetics, and PTCy immune phenotyping, with particular emphasis on T-cell subsets (NCT03555851). We anticipate the results of this study will provide a better understanding of the pharmacologic basis for GVHD prevention with PTCy, further allowing for personalized dosing strategies to improve treatment outcomes. ●

Disclosure

The authors have no conflicts of interest to disclose.

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