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Review article

Using cyclophosphamide in inflammatory rheumatic diseases

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ABSTRACT

Cyclophosphamide (CYC), primarily introduced into clinical practice as an anti-cancer substance, is a potent immunosuppressive drug. Today, it is used in a number of organ- or life -threatening autoimmune diseases such as systemic vasculitides or connective tissue diseases. While being effective, CYC has a small therapeutic index and is associated with significant toxicity. CYC has been used in oncology in a variety of diseases and a lot of data has been derived from this area. This knowledge is often extrapolated to the rheumatologic settings. However, besides some similarities substantial differences between these two specialties considering the underlying diseases as well as the kind of application of the drug exist. The aim of the present review is to describe the general characteristics of the use of CYC from the rheumatologist's point of view, including pharmacologic and pharmacokinetic properties, drug interactions, toxicity and possible preventive and/or therapeutic measures; all of which are important to consider when using this particular drug in the treatment of inflammatory rheumatic diseases.

1. Introduction

Alkylating agents such as cyclophosphamide (CYC) were developed and introduced into clinical medicine in the 1950s. They were primarily designed as anti-cancer drugs [1]. History has shown that CYC is one of the most potent immunosuppressive drugs available. Therefore, today CYC is being used in cases of life- or organ-threatening conditions, such as inflammatory and autoimmune ailments. These conditions include systemic vasculitides such as anti-neutrophil cytoplasmic antibody (ANCA) associated systemic vasculitis [2,3] or corticosteroid-resistant polyarteritis nodosa [4], systemic lupus erythematosus (SLE) with severe visceral affection (e.g., central nervous system, heart, lung) [5–7] as well as lupus nephritis [8] or pulmonary manifestations of systemic sclerosis [9]. CYC has also been used in rheumatoid arthritis, but due to its toxicity it is irrelevant compared to other disease modifying antirheumatic drugs (DMARDs) [10]. As CYC, a drug with a small therapeutic index, has been used in oncology in a variety of diseases lots of information have been gained in that field. Knowledge experienced in oncology is often extrapolated to rheumatologic settings. However, besides some similarities there also exist substantial differences between these two specialties considering the underlying diseases as well as the kind of application of the drug. The aim of the present review is to describe the general characteristics of the use of CYC from the rheumatologist view point, which are important to consider when using this particular drug in inflammatory rheumatic diseases.

2. Pharmacology

CYC is a prodrug, meaning that it is administered and transported inactively and is oxidized to 4-hydroxycyclophosphamide by the mixed function oxidase system of the liver [11]. 4-hydroxycyclophosphamide enters cells and spontaneously decomposes to phosphoramide-mustard and acrolein [12], the last a highly electrophilic α,β-unsaturated aldehyde, being accountable for many toxic side effects, as described below [13] (Fig. 1).

At a physiological pH of 7.4, phosphoramide-mustard has a significant alkylating activity [14] that exerts its cytotoxic effects through the covalent linkage of alkyl groups of the DNA [15]. The so formed inter-strand crosslink creates denaturation-resistant DNA fractions ultimately leading to the inhibition of DNA replication and consecutive apoptosis [16]. This effect applies not only for cancer cells, but also for overactive immune competent cells that are found in various autoimmune diseases.

In 1973, *Alan Winkelstein* demonstrated that CYC is an effective inhibitor of cell mediated immune response and leads to a depletion of lymphocytes in the peripheral blood and tissue [17]. In vivo monocyte function is also affected by CYC leading to a decrease in IL-1 and TNF production via direct effects and indirect effects through lymphocytic or hematopoietic systems that activate monocytes [18].

It has been shown that CYC has significant influence on the activation and differentiation of B-cells leading to an alteration of the antibody

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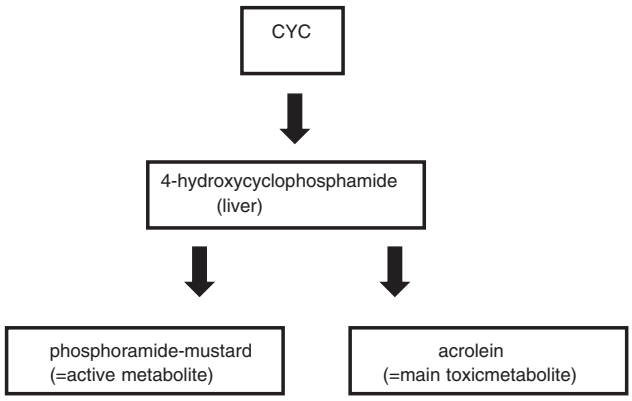

Fig. 1. Metabolism of CYC. While phosphoramide-mustard is the active metabolite, acrolein is the major metabolite that causes bladder irritation and cystitis. It predisposes the toxic patients to bladder mucosal atypia and cancer.

mediated humoral immune response. This is true for the T-cell dependent as well as T-cell independent B-cell activation [19]. A reduced number or an impaired function of regulatory T-cells, which are responsible for suppressing immune responses and serve as a cornerstone of "self-tolerance", has been linked to the development of several rheumatic disorders [20]. Even though CYC treatment causes a loss of $CD4^+$, $CD25^+$ and $Foxp^{3+}$ T-regulatory cells, CYC can be used for treating severe autoimmune conditions [21].

3. Pharmacokinetics

CYC can be administered orally, intravenously or even subcutaneously [22]. Struck et al. showed in a randomized crossover trial that there are no significant differences in oral versus I.V. treatments, suggesting equal efficacy for these two routes of CYC administration [23]. CYC is almost completely absorbed in the gastrointestinal tract [24] and distributed throughout the body. Only a small fraction of intact CYC is protein bound, but studies have shown that a major fraction of its alkylating metabolites are plasma protein bound. Peak free alkylating metabolite levels occurred 2 to 3 h after therapy. The mean half-life in patients without prior drug exposure is 6.5 h [25].

Bioactivation of CYC requires the activity of cytochrome P450 (CYP) enzymes: the generation of 4-hydroxycyclophosphamide is mediated by various isoforms (CYP2A6, 2B6, 2C8, 2C9, 2C19, 3A4 and 3A5), detoxification of the metabolites is mainly achieved through NADPH-mediated oxidation by various aldehyde dehydrogenases (ALDH) but also by conjugation with glutathione by various glutathione S-transferases (GST) [26]. Considering the fact that CYC has a small therapeutic index, it is important to understand that the metabolism of CYC can be affected by other drugs taken at the same time. This includes substances that lead to an acceleration or deceleration of the biotransformation by affecting the mixed function oxidase system [27] and substances that interfere with other arms of the metabolic pathways [28]. Genetic polymorphisms in the CYP, GST and ALDH families of enzymes have been found to impact response and/or toxicity associated with cyclophosphamide based therapies [26]. The majority of CYC is excreted into urine. Less than 1/5 is excreted unchanged and correlates with creatinine clearance. The rest has alkylating activity; breath and fecal excretion are negligible [25].

Not surprisingly the clearance of CYC and its cytotoxic metabolite phosphoramide-mustard is reduced in patients with impaired renal function. Therefore, the dose and timing of administration have to be adapted to underlying renal insufficiency or ongoing hemodialysis [29,30]. According to the Drug manual of Endoxan® (Baxter), a CYC dose reduction of 50%, in the case of a glomerular filtration rate below 10 ml per minute, is recommended. It has also been demonstrated that the mean total body clearance of CYC is reduced in severe liver failure and could lead to an accumulation. Therefore, a dose reduction may be required [31].

3.1. General aspects and dosing

Since oncology is the major field of CYC use, a great deal of data and many experiences are derived from that specialty and are "extrapolated" to rheumatology. However, there are substantial differences in dosage and duration of treatment. Furthermore, CYC is combined with different drugs than in malignancies.

On the one hand, the purpose of a CYC regimen is to gain swift control of disease activity and, on the other hand, to prevent toxic side effects that cohere with a long term CYC treatment. Thus, strategies have been developed to minimize CYC exposure. At the beginning of treatment CYC is usually given more frequently and/or at a higher dosage ("induction") for several months. Thereafter, dosing intervals are stretched or – more frequently – CYC is switched to less toxic immunosuppressant ("maintenance") [32]. While CYC has a strong potential to accomplish remission, its toxicity may outweigh a long-term treatment for remission maintenance [33].

For example, daily oral CYC and intravenous pulse therapy did not differ in time to remission or portion of remission in ANCA associated vasculitis [34]. The median time to remission was three month. However, I.V. CYC caused fewer episodes of leucopenia, which is likely due to a lower cumulative dose [34].

For IV CYC the commonly used dosage is 15 mg/kg given every 2 to 3 weeks (with adaption of dose according to age and kidney function), usually for three to six month [34,35]. The usual initial dose for oral CYC is 2 mg/kg/day given for the same time span [34,36–38]. The duration of treatment is in part dependent on the individual response of the patient.

In clinical practice there are several options available for remission control after remission has been achieved by CYC. After entering remission by intravenous CYC, it was demonstrated that azathioprine (AZA) and methotrexate (MTX) are efficient alternatives for maintaining remission in patients with granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) and microscopic polyangiitis, while having a similar toxicity profile [39]. Mycophenolate mofetil (MMF) is less effective in AASV than AZA for maintaining disease but may be an option in selected patients [40].

As a further example, a sequential therapy with intravenous CYC followed by maintenance therapy with MMF or AZA in patients with lupus nephritis, proved to be safer and more efficacious than long-term therapy with intravenous CYC [41].

According to the Euro-Lupus Nephritis Trial [42] a fixed dose of 6 fortnightly I.V. CYC pulses at a dose of 500 mg compared to 8 I.V. CYC pulses at an initial dosage of 500 mg/m^2 of body surface (sequential dosages were adapted) within a year (six monthly pulses followed by two quarterly pulses) are equally effective, with less infectious side effects. Recently two societies issued recommendations for the treatment and management of lupus nephritis, including the place of CYC. Hahn et al. presented the recommendations of the American College for Rheumatology (ACR) [43] Bersias et al. presented the recommendations from a collaboration of the European League Against Rheumatism and the European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) [44]. For initial treatment of lupus nephritis class III and class IV the ACR recommends either IV CYC or MMF in combination with steroids. If CYC is chosen one of two regimens can be used: High-dose CYC is given in a dose of 500–1.000 mg per square meter body surface area every month for a total of 6 boli. Low-dose CYC is given as a fixed dose of 500 mg I.V. every 2 weeks for a total of 6 boli. This regime should mainly be used in white patients with European ancestry. It should be noted that this regime has not been extensively studied in other populations. As Black or Hispanic lupus patients seem to respond less to CYC the high-dose regime should be favored in those particular patient groups if CYC is chosen instead of