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Short communication

Methotrexate - an old drug with new pharmaceutical formulations and new indications

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Introduction

Methotrexate (MTX), also known as amethopterin is an antifolate and an antimetabolite drug, a chemical analogue of folic acid developed by Yellapragada Subbarao of Lederle (Rossi, 2013). MTX was first administered to children with acute lymphoblastic leukemia (ALL) in 1948. MTX became the first drug that induced remission. Remissions were short, but the principle was clear, antifolates could suppress proliferation of malignant cells, and could thereby re-establish normal bone-marrow function. MTX received FDA approval in 1953. Since that time it has been used worldwide for a variety of medical interventions.

Firstly, MTX has been used as a parenteral formulation for cancer treatment. The use of MTX in the treatment of psoriasis and rheumatoid arthritis dates from the 1960s. From the late 1970s to the early 1980s, many rheumatologists were reporting their experiences with MTX use in rheumatoid arthritis treatment (Ward, 1985). MTX can be given orally or by intravenous, intramuscular or subcutaneous injection (Jundt et al, 1993). Intramuscular, intravenous or subcutaneous administration is usually reserved for patients with poor oral bioavailability of the drug or poor adherence to oral therapy, or when the cost is an issue. Weekly dosing of MTX is recommended. More frequent administration than weekly increases the risk of toxicity. The entire dose can be administered at once or divided into three doses taken over a 24-hour period (i.e., every eight hours). MTX should never be given in daily doses. During the 1980's and 1990's many studies were done with MTX to determine if it could suppress the growth of a tubal or ectopic pregnancy. Researchers discovered that MTX could be given as a safe treatment for the ectopic pregnancy treatment cured without surgery. Further research found that MTX could also be used to induce a chemical abortion. A small percentage of the cases required surgical intervention. The benefit of a MTX-induced abortion is that if there is an unknown tubal pregnancy it will be treated. MTX has also been found efficacious in the treatment of other diseases, including psoriasis, asthma, systemic lupus erythematosus, Crohn's disease, myositis and vasculitis. Many physicians use MTX for its steroid-sparing properties in patients with asthma and others who may have side effects related to corticosteroid use. The key of the success of MTX in the treatment any of these diseases (with the exception of ALL) is the recognition that low-dose therapy achieves efficacy while minimizing side effects (Moss, 1995).

MTX is a toxic medication, but if it is dosed correctly and monitored appropriately, its toxic effects can be minimized. These effects are categorized as minor or major. Minor toxic effects such as stomatitis, malaise, nausea, vomiting, diarrhea, headaches and mild alopecia are not life threatening but occur in 20 to 30 percents of patients. Other effects in this category include fatigue, mood alteration, dizziness, fever, myalgia and polyarthralgia. Most minor toxic effects are associated with depletion of folate. Folate supplementation with 1 mg daily or 7 mg once weekly should be considered for all patients. Studies show that low-dose folate does not interfere with the efficacy of MTX (ACRM, 1996). Most rheumatologists advise patients to avoid taking the folate dose on the same day as the MTX dose. Often, minor toxic effects respond to a re-

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duction in the MTX dose or an adjustment in the dosing schedule. Major toxic effects of MTX, such as hepatic, renal, pulmonary and bone marrow disorders, occur less frequently than the minor effects but may be life threatening.

In order to improve therapeutic efficacy and the comfort of the application of MTX, new pharmaceutical formulation is ongoing. Controlled release of MTX has been achieved by several techniques, but mostly in in vitro and preclinical animal models. Formulations of MTX that have been recently developed in order to improve cancer treatment include injectable thermosensitive hydrogels containing MTX-loaded chitosan-based microspheres, folic acid-chitosan-MTX core-shell nanoparticles, thermosensitive systems prepared on biocompatible polymer Pluronic F-127 as a vehicle, MTX-loaded alpha-lactalbumin microparticles, MTX-monoclonal antibody conjugates, MTX intercalated in a nanoceramic vehicle magnesium aluminium layered double hydroxide, coated with poly(D,L-lactide-co-glycolide) (PLGA). Most of these pharmaceutical formulations have demonstrated superiority when compared to conventional formulations of MTX in terms of localized drug delivery, long-term sustained drug release, and good biocompatibility (Beidokhti et al., 2016). Novel topical formulations of MTX have been also evaluated for the potential use in the treatment of psoriasis. Some of these formulations with enhanced skin penetration of MTX include microemulsions, nanogels, niosomes, liposomal hydrogels, deformable liposomes and solid lipid nanoparticles (SLN) (Avasatthi et al., 2015). The latest topical formulations of MTX for the treatment of psoriasis prepared as nano-vesicles use mostly bioadhesive surfactant systems containing polysorbate 60 or 80 as surfactants. NLC-based smart gel of MTX composed of lipids, surfactant Tween 80 and co-surfactant PEG 400, was formulated for intra-articular administration that could give site-specific delivery of a drug to the rheumatic joints (Shinde et al., 2016). MTX was also formulated in transdermal patches with different ratios of ethyl-cellulose and hydroxypropylmethyl-cellulose, and permeation enhancers Tween-80, Span-80, dimethyl sulphoxide (DMSO), and isopropyl myristate. These transdermal patches were evaluated for in vitro release, ex vivo permeation and pharmacokinetics in vivo, and all formulations exerted improved bioavailability in comparison to MTX without enhancers (Rama et al., 2012).

In summary, MTX plays a significant role in the treatment of various diseases, but toxicity remains the main issue of the use of MTX. Therefore, novel pharmaceutical formulations, which have reduced toxicity, better pharmacokinetic properties and targeted delivery, have emerged. Promising results have been obtained, but mostly in in vitro and in vivo animal studies. Therefore, these new formulations and drug delivery systems of MTX need to be further evaluated, especially in clinical settings.

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