Methotrexate for Use in Pediatric Populations

Methotrexate

Methotrexate has many mechanisms of action, but its main known mechanism is as an inhibitor of the enzyme dihydrofolate reductase.


Mechanisms of Action:

High Dose Mechanisms of Action: High doses of methotrexate are used for anti-proliferative activity on cells by inhibiting dihydrofolate reductase. Dihydrofolate reductase is an enzyme involved in thymidylate and purine synthesis by converting dihydrofolate to tetrahydrofolate, thereby replenishing reduced folates (Wallin, 2006; Goldman and Matherly, 1985). Dividing cells utilize reduced folates, such as tetrahydrofolate, to synthesize purines and thymidines (Wallin, 2006). Purines and thymidines are precursors for nucleotide synthesis, which are necessary for DNA replication (Chu and Sartorelli, 2007). Malignant cells are rapidly dividing and hence have a greater need for reduced folates in order to maintain replication throughout cell divisions. Methotrexate depletion of reduced folates stops synthesis of thymidine, thereby stopping replication (Chu and Sartorelli, 2007). This ultimately leads to cell death and inhibition of cellular proliferation (Chu and Sartorelli, 2007). High doses are needed for anti-proliferative effects because tetrahydrofolate synthesis occurs until greater than 95% of dihydrofolate reductase is inhibited. Furthermore, methotrexate needs to work intracellularly in order to affect dihydrofolate reductase. High doses are required in order to saturate the pump that transports methotrexate into the cell (Wallin, 2006). Methotrexate competitively inhibits dihydrofolate reductase because it has a higher affinity for dihydrofolate reductase than the natural substrate, dihydrofolate (Goldman and Matherly, 1985; Chu and Sartorelli, 2007).

The significance of reduced folates for cellular metabolism is as a source of functional groups for intracellular reactions. Reduced folates specifically within the thymidylate synthesis pathway are a source of a methyl group. For example, the enzyme thymidylate synthetase transfers a methyl group from 5-methylenetetrahydrofolate (a reduced folate) to deoxyuridylic acid monophosphate (dUMP) in order to synthesize deoxythymidylate monophosphate (dTMP) (Chu and Sartorelli, 2006). Reduced folates within the purine synthesis pathway are a source of formyl groups. For example, the enzymes glycaminid ribonucleotide transformylase and aminomimidazole carboxamidase transformylase transfer formyl groups from the reduced folate N(10)-formyltetrahydrofolate to initiate synthesis of the purines, adenine and guanine (Walling, 2006). Depletion of purines also contributes to stalling replication and encouraging cell death.
Methotrexate is also polyglutamated within the cell. Polyglutamation of methotrexate within the cell by the enzyme folyl polyglutamate synthetase increases the anti-proliferative effects of methotrexate by making it difficult for the cell to transport the methotrexate out of the cell (Jolivet and Chabner, 1983; Treon and Chabner, 1996; Chabner et al., 1985). Polyglutamated methotrexate also inhibits enzymes involved in DNA replication mentioned above such as, thymidylate synthetase, glycaminide ribonucleotide transformylase, and aminoisimidazole carboxamide transformylase (Chabner et al., 1985). Hence, polyglutamated forms of methotrexate exert similar inhibitory effects on the same enzymes as methotrexate and are kept in the cell longer. This amplifies and enhances the effects of methotrexate (Jolivet and Chabner, 1983). Polyglutamation of methotrexate only occurs at high doses because polyglutamation of methotrexate within cells occurs when doses are a minimum of 2 uM (Jolivet and Chabner, 1983).

Intermediate and Low Dose Methotrexate Mechanisms of Action: Intermediate and low doses of methotrexate are mostly used for immunomodulatory effects. However, a recent study showed intermediate dose methotrexate is effective for relapse acute lymphoblastic leukemia (ALL) (von Steckelberg et al., 2008). The complete mechanism for how methotrexate modulates the immune system is not fully elucidated, but some theories propose that its cytotoxic effect may have an immunomodulatory effect by having a greater cytotoxic effect on lymphocytes as they have a high turnover rate (Wallace, 1998; Segal and Sneller, 1997). This is a reasonable proposal considering methotrexate inhibits dihydrofolate reductase, thereby lowering the amount of reduced folates for cells. Decreased concentration of reduced folates inhibits thymidine and purine synthesis, resulting in inhibition of replication. The replication block ultimately results in cell death (Wallin, 2006). Methotrexate’s effect on cell death would greatly affect any cell type that has a high turnover rate. It has also been postulated that the immunomodulatory effect may be due to its inhibition aminoisimidazolecarboxamide ribonucleotide transformylase and thymidylate synthetase, thereby decreasing polymorphonuclear chemotaxis (primarily neutrophil chemotaxis) (Furst and Ulrich, 2007). A few reports have also found that cytokine transcription factors are also lowered (Kamel et al., 1993); however, the exact mechanism of cytokine reduction needs to be fully elucidated.

Pharmacokinetics:
Absorption: Oral methotrexate is on average 30%; variable at low doses. Intramuscular and subcutaneous administration of methotrexate: completely absorbed (Fleischer et al, 2007). For distribution, it is noteworthy that methorexate via intramuscular injection or oral route do not provide therapeutic concentrations in the CSF (Fleischer et al., 2007). Methotrexate is metabolized in the liver to 7-hydroxymethotrexate (Fleischer et al., 2007). Protein binding is 50% to 60% (Bleyer, 1977). Time to peak serum concentration is 0.5-4 hours for oral methotrexate, whereas it is 0.5-2 hours for parenteral administration (). The half-life is for low dose methotrexate (<30 mg/m$^2$) 3-10 hours and high dose methotrexate 8-15 hours (Bleyer, 1977). Methotrexate is eliminated in feces and primarily excreted unchanged in urine (90%) via glomerular filtration and active secretion by the renal tubule (Gianni et al., 1992; Fleischer et al., 2007). 1% to 11% of a methotrexate dose is excreted as the 7-hydroxy metabolite (Bleyer, 1977).

Therapeutic Uses in Pediatrics:
Methotrexate is historically and currently indicated for use in pediatric populations with various neoplastic disorders, such as acute lymphocytic leukemia, meningeal leukemia, osteosarcoma, some brain tumors, and non-Hodgkin’s lymphoma. These neoplastic indications are well established and researched. Hence, I will only highlight a few studies or standard of care. Methotrexate for neoplasms or leukemias almost always require combination therapy (Bleyer, 2007).
High dose methotrexate as a component of chemotherapy for acute lymphoblastic leukemia (ALL) has been used extensively in children and adults (von Stackelberg et al., 2008; Pui et al., 2004; Reiling et al., 1994; Brenner and Evans, 2002). Pui, an ALL expert at St Jude’s children’s hospital in Memphis, Tennessee, reports methotrexate is one of the most effective agents for pediatric ALL and has the option of a toxicity rescue with leucovorin (Pui et al., 2004). As such, it is a component of most current ALL frontline treatment worldwide (Pui et al., 2004; von Stackelberg et al., 2008). Leucovorin is folinic acid, a tetrahydrofolate derivative that does not require dihydrofolate reductase for its conversion within a cell. Hence, if the lack of reduced folates from methotrexate becomes too toxic, Leucovorin (folinic acid) bypasses the inhibition of dihydrofolate reductase, allowing some normal replication to occur (Jardine et al., 1996). A recent study for the treatment of first relapse ALL in children has also found that intermediate dose methotrexate is as effective as high dose methotrexate for ALL (von Stackelberg et al., 2008). Specifically, von Stackelberg et al. found that at a median follow-up of 14.1 years, the 10 year event-free survival probability was .36 (± .04) for the intermediate dose group (n=114) and .38 (± 04) for the high dose group (n=128, p=.919) (2008). Thus, it is possible that intermediate doses may be possible in certain patient subgroups for ALL.

In a non-randomized trial of 118 children given high dose methotrexate for ALL, 114 achieved complete remission with a dose of 2 g/ m$^2$/ infused over 24 hours every three weeks and every three weeks for 3 (Koizumi et al., 1991). This regimen was consistent with current combination therapy as other agents were included and leucovorin was used as rescue for toxicity.

For meningeal leukemia and lymphomatous meningitis intrathecal methotrexate followed by high dose methotrexate infusion with other chemotherapeutic agents such hydrocortisone and ara-C is the standard of care throughout the world (Ruggiero et al., 2001; Blaney et al., 1991). Chamberlain at the University of California, San Diego reported that in follow-up studies of all of the children (out of 15 children) with lymphomatous meningitis were disease free at 5 year follow-up from combination chemotherapy with high dose methotrexate, whereas the children with carcinomatous meningitis died despite therapy (1997).

Standard of care around the world for the chemotherapy segment for osteosarcoma involves various combinations with methotrexate. One regimen involves high dose methotrexate followed by leucovorin rescue (Chi et al., 2004). Other combinations involve high dose methotrexate with doxorubicin and cisplatin (Goorin et al., 1987). This combination is particularly recommended for children (protocol of the American and European Osteosarcoma study group, 2007; Goorin and Maki, 2007). Currently a large international study for children is being conducted under the protocol of the American and European Osteosarcoma study group testing the addition of alpha interferon in addition to high dose methotrexate (2007).

Methotrexate has many uses as an immune modulator for rheumatologic and other inflammatory diseases. Methotrexate is considered a second line treatment of juvenile idiopathic arthritis (JIA) after 1st line combination of non-steroidal anti-inflammatory drugs (NSAIDs) and steroids (Haines, 2007; American College of Rheumatology, 1993). An initial placebo-controlled double-blind study was performed in pediatric populations in 1986 through 1992 for pediatric populations, showing that methotrexate was as effective as steroids and NSAIDS for children with juvenile idiopathic arthritis (JIA) (Giannini et al., 1992). In 1993, the Pediatric Rheumatology Collaborative Study Group (PRCSG) published a meta-analysis of three clinical trials that were double-blind placebo-controlled comparing the treatments of d-penicillamine, hydroxychloroquine, oral gold, 5 mg/m$^2$ of methotrexate, and 10 mg/m$^2$ of methotrexate. (Giannini et al., 1993). PRCSG meta-analysis found that only 10 mg/m$^2$ of methotrexate showed efficacy, with 50% of children having a at least a 50% improvement on the standardized composite index defined by the American College of Rheumatology Pediatric indexes (Giannini et al., 1993; Haines, 2007). According to studies at
New York University Hospital for Joint Diseases, a retrospective analysis by Gottlieb et al. of 101 patients with JIA found that 48 developed a response defined as “absence of synovitis and normalization of laboratory parameters while on medication” (Gottlieb et al., 1997; Haines, 2007). Gottlieb et al study also found that in these 48 responders to methotrexate, upon withdrawal of methotrexate 24 of these responders had a relapse of disease (Gottlieb et al., 1997).

Methotrexate is also used for an inflammatory condition called uveitis, which can occur on its own or in conjunction with other inflammatory conditions, such as a component with JIA, sarcoidosis, ankylosing spondylitis, and ulcerative colitis. Uveitis must be treated in pediatric populations due to an increased risk of progression to band keratopathy, posterior synchiae, secondary cataract and glaucoma, macular edema, and visual loss (Wright and Cron, 2007; Rosenberg et al., 2004). Yu et al. examined a cohort of 23 children with JIA and uveitis that did not respond to topical or systemic steroid (2005). Patients were given methotrexate or methotrexate combined with cyclosporine, azathioprine, or cyclophosphamide. Methotrexate alone controlled inflammation in 48% of cases, but another 48% needed the addition of cyclosporine, azathioprine, or cyclophosphamide. Foeldvari and Wierk in a retrospective examination of 25 JIA associated uveitis patients found that 84% of these 25 went into remission on a dose of 10 – 25 mg/m²/week for 4.5-6 months (2005).

According to Thomas Lehman MD, a pediatric rheumatologist at the Hospital of Special Surgery, methotrexate use in systemic lupus erythematosus is reserved for children with cyclophosphamide-resistant or relapsed class IV nephritis when the maximum dose of cyclophosphamide has already been attempted (Adams et al., 2007). It is important to note that although all five patients significantly improved on the combination with methotrexate, that it was only five patients that improved according to their C3 levels, SLEDAI scores, and creatinine levels (Adams et al., 2007).

Methotrexate is also often used in pediatric populations for the inflammatory bowel diseases, Crohn’s disease and ulcerative colitis (Hommes et al., 2007; Feagan et al., 1995). It is most commonly used in Crohn’s disease that is refractive to steroid treatment and thiopurines. A randomized placebo-controlled blind trial found that 80% of 42 children responded or entered remission with methotrexate (Uhlen et al., 2006). Although reviews of data suggest that methotrexate is helpful in steroid refractory Crohn’s disease, a Cochrane Database systematic review of the data for methotrexate use in ulcerative colitis to not be effective in remission induction (Chande et al., 2007). The only methotrexate use found to be beneficial for ulcerative colitis, was ulcerative colitis associated uveitis (Chande et al, 2007, Cron et al, 2003).

Methotrexate is often used in children for psoriasis and psoriatic arthritis based on extrapolating doses from adult studies (Kaur et al., 2008); however, recently some studies have examined methotrexate for psoriasis in children. Kaur et al examined 29 children with psoriasis refractory to other treatments such as corticosteroids (2008). Response was evaluated as based on the psoriasis area and severity index (PASI). A grade of a “good response” was defined as a greater than 50% decrease on PASI and a grade of “excellent response” was defined as a greater than 75% decrease on PASI. Kaur et al found that 22 out of the 24 children responded in the excellent response category, 5 could not be included in data analysis and 2 had no response (2008). Kaur et al reported a mean cumulative dose of 215 mg. However, the individual dosing was not reported (Kaur et al., 2008).

Methotrexate is often used for glucocorticoid refractory sarcoidosis or severe organ failure sarcoidosis (Baughman et al, 2008; Baughman et al, 2000). Current standard of care for both adults and children is if prednisone is not able to be tapered in sarcoidosis to less than or equal to 10 mg per day of prednisone, a cytotoxic agent such as methotrexate is added (Baughman et al., 2008). In the Baughman et al. double blind randomized trial of methotrexate use in
acute and chronic sarcoidosis, methotrexate improved pulmonary and neurological involvement in chronic sarcoidosis (2000). In a follow-up study of methotrexate use for sarcoidosis, approximately two-thirds of 91 sarcoidosis patients responded to treatment with the addition of methotrexate (Vucinic, 2002; Baughman et al., 2008; Baughman et al., 2000). Furthermore, a review of data from sarcoidosis treatment centers around the United States, reported the best clinical outcomes for pulmonary, neurological, and ocular involvement with methotrexate versus other steroid sparing cytotoxic agents (Baughman et al., 2008).

Methotrexate is also treatment for eosinophilic fasciitis in children (Ortega-Loayza et al., 2008). Eosinophilic fasciitis is very rare with approximately 30 children having been reported worldwide. Although rare, Ortega-Loayza et al have reported that glucocorticoids and methotrexate effective in those not completely glucocorticoid responsive (2008).

Methotrexate is also used as a steroid sparing agent for Henoch Schonlein purpura vasculitis and other vasculitides (Rettig and Cron, 2003; Chen and Carlson, 2008; Cron et al., 1999). This is currently standard of care in the United States and Canada for pediatric vasculitides (Cron et al., 1999; Rettig and Cron, 2003). Methotrexate is also used in pediatric Wegener’s Granulomatosis (Aikikusa et al., 2007). Methotrexate is often used for intravenous immunoglobulin (IVIG) refractory pediatric Kawasaki’s disease with good response (Ahn and Kim, 2005; Lee et al., 2002; Kim et al., 2008). Most have been case studies or retrospective analysis (Ahn and Kim, 2005; Lee et al., 2002; Kim et al., 2008).

**Dosing:**

For neoplastic disorders, the doses vary. Goorin et al in the pediatric oncology group trial recommends for pediatric osteosarcoma doses of 12 mg/m$^2$/ of methotrexate at weeks 0, 1, 5, 6, 13, 14, 18, 19, 23, 24, 37, 38 followed by leucovorin 15 mg po every six hours for 10 doses (2003, 2007). Surgery follows with doxorubicin and cisplatin.

Acute Lymphocytic Leukemia has dose ranges that range in pediatric populations from 1g/ m$^2$ to 8 g/m$^2$ (von Stackelberg et al., 2008; Brenner and Evans, 2002). The dose depends on the combination and whether it is involved in the induction phase of chemotherapy (von Stackelberg et al., 2008). Meningeal leukemia or lymphomatous meningitis doses of intrathecal methotrexate are 2 g/ m$^2$/week, followed by systemic in fusion of methotrexate within the range of 1 g/ m$^2$- 5 g/ m$^2$ with the option of leucovorin rescue (Blaney et al, 1991; Ruggiero et al., 2001). Fleischer et al., give doses intrathecally every 2-5 days for meningeal leukemia. The doses Fleischer et al. recommend are 6 mg for a child under 1 year of age, 8mg for a 1year old. 10 mg for a 2 year old, and 12 mg for any child over the age of 3 (2007). Gal and Reed give the range of 1-30 g/ m$^2$ infused over 6-42 hours (2007).

For juvenile idiopathic arthritis, studies have shown positive results from 10 mg/m$^2$/week to 40 mg/m$^2$/week of methotrexate. However, Rupert et al. studied 80 children with JIA that had not responded to standard treatment of NSAIDS and steroids, in two groups (2004). One group received 8-12 mg/m$^2$/week dose of methotrexate for 6 months and the other group received 30 mg/m$^2$/week of methotrexate. At the end of the 6 months, Rupert et al found that 25/40 in the 8-12 mg/m$^2$/week dose of methotrexate and 23/40 in the 30 mg/m$^2$/week dose of methotrexate had a 50% or greater improvement on the American College of Rheumatology pediatric index (2004). Hence, there was no difference in effect based on dose in this population. Interestingly, Haines notes that in the Rupert et al. study the side effects were similar in the 8-12 mg/m$^2$/week dose of methotrexate group and 30 mg/m$^2$/week dose of methotrexate group (2007; Rupert et al., 2004). Thomas Lehman MD, an expert pediatric rheumatologist at the Hospital of Special Surgery utilizes a range of 10 mg/m$^2$/week to 40 mg/m$^2$/week ranges depending on the severity and resistance of the case (2008).
For uveitis, Wright (pediatric ophthalmologist) and Cron (pediatric rheumatologist at Children’s Hospital of Philadelphia) recommend 7.5 mg to 25 mg weekly when given subcutaneously (2007; Jabs et al., 2000). If giving doses of greater than 15 mg/m²/week, parenterally has better absorption (2007).

For Crohn’s disease, methotrexate is given in a range from 15 mg/m²/week to 25 mg/m²/week subcutaneously for 3-6 months. Then switching to parenteral administration (Rufo and Bousvarous, 2006; (Hommes et al., 2007).

For sarcoidosis, the recommended dose for glucocorticoid refractory sarcoidosis is 10-15 mg/week (Baughman et al., 2008).

For the various vasculitides, including Henoch Schonlein purpura, Kawasaki’s disease, and Wegener’s granulomatous, the recommended doses are in the range of 5 to 20 mg/m²/week depending on the individual child’s response (Rettig and Cron, 2003; Cron et al., 1999; Akikusa et al., 2007).

Interactions: Folate supplementation may decrease drug response and folate deficiency states may increase toxicity (Flesicher et al., 2007) and milk-rich foods may decrease absorption (Fleischer et al., 2007). Avoid nephrotoxic agents (e.g. cisplatinum), NSAIDs (at high doses), highly protein bound drugs (sulfonamides, phenytoin etc.). TMP/SMZ may increase bone marrow suppression with methotrexate use (Fleischer et al., 2007). Penicillins may decrease clearance (Fleischer et al., 2007). Methotrexate may increase the clearance of theophylline (Fleischer et al., 2007)

Therapeutic Monitoring: CBC with differential and platelet count, creatinine clearance, serum creatinine, BUN, hepatic function tests, serum electrolytes, urinalysis, plasma methotrexate concentrations (see Leucovorin rescue graph> to evaluate plasma methotrexate concentration versus leucovorin rescue dose); periodic liver biopsy for psoriatic patients receiving long-term treatment; chest x-ray; pulmonary function tests if methotrexate-induced lung disease is suspected (Fleischer et al., 2007)

Contraindications: Contraindicated in renal and liver disease as well as immune deficiencies (Shimasaki et al., 2008). Methotrexate is contraindicated in neonates because it may cause a gasping syndrome (Fleischer et al., 2007). It is noteworthy that researchers in 2007-2008 have been finding certain polymorphisms associated with methotrexate toxicity and may have implications for contraindication (Shimasaki et al., 2008). However, the fact that there is an antidote to toxicity from methotrexate, leucovorin rescue, makes methotrexate ideal compared to other cytotoxic medications (Jardine et al., 1997).

Adverse Reactions/Side Effects:

Various side effects have been reported. Studies in rheumatoid arthritis, juvenile idiopathic arthritis, sarcoidosis, and psoriasis have reported that nausea, vomiting, diarrhea, and leucopenia are the most common adverse reactions that usually respond to dose reduction (Baughman and Lower, 1999; Roenigk et al., 1982; Cheng, 2008). Neutropenia specifically has been frequently documented in children (Cheng, 2008). Pulmonary toxicity is another, but less common adverse reaction (Zisman et al., 2001). Increased risk for opportunistic infections is also a possible risk (Baughman and Lower, 2005). Anemia has also often been noted (Baughman et al, 2008; Cron et al., 1991).

The American College of Rheumatology has documented in double blind, randomized clinical trials and case studies the risk of hepatotoxicity associated with methotrexate use and created guidelines for monitoring hepatotoxicity with methotrexate use (Kremer et al., 1994). Most
studies including those for cancer and other inflammatory diseases report hepatotoxicity being the greatest risk from methotrexate (Domenech et al., 2008).

Oral and digestive mucositis has been documented in children with use of methotrexate often due to enterocyte mitosis arrest (Cheng, 2008; Sood, 2007). Skin reactions have occurred, such as urticaria (Demircioğlu et al., 2008; Cron et al., 1991). Photosensitivity reactions are common (Gal and Reed, 2007) and an increase or decrease in skin pigmentation (Gal and Reed, 2007) Cognitive disability or attention disorders have been noted in some children with ALL with high dose methotrexate (Moore et al., 2008; Krull et al., 2008). Headaches, seizures are often reported (Gal and Reed, 2007). Other systemic manifestations such as fever, malaise, weightloss are common (Gal and Reed, 2007).

Renal dysfunction has been reported with high dose methotrexate use for leukemias (Grönroos et al., 2008). Specifically in 1-10 year long term follow-up of 28 children treated with high dose methotrexate for pediatric acute lymphocytic leukemia and lymphoma with examination of renal functions such as GFR before treatment and after, high dose methotrexate was associated with significant decline in GFR in children (Grönroos et al., 2008). Cystitis and hyperuricemia are also common for high dose methotrexate (Gal and Reed, 2007).
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