Methotrexate

Class: Antimetabolite (Antifolate)

Indications :

_Acute lymphoblastic leukemia (ALL) maintenance treatment

_ ALL meningeal leukemia (prophylaxis and treatment)

_treatment of trophoblastic neoplasms (gestational choriocarcinoma, chorioadenomadestruens andhydatidiform mole)

_breast cancer

_head and neck cancer (epidermoid)

_cutaneous T-Cell lymphoma (advanced mycosis fungoides)

_lung cancer (squamous cell and small cell)

_advanced non-Hodgkin's lymphomas (NHL)

_osteosarcoma

Available dosage form in the hospital: 2.5 MG , 10 MG TAB

Trade name : Rheumatrex , Trexall

Doses:

Note: Doses between 100-500 mg/m^2 **may require** leucovorin calcium rescue. Doses >500 mg/m^2 **require** leucovorin calcium rescue: I.V., I.M., Oral: Leucovorin calcium 10-15 mg/m^2every 6 hours for 8 or 10 doses, starting 24 hours after the start of methotrexate infusion. Continue until the methotrexate level is ≤0.1 micromolar (10^{-7} M). Some clinicians continue leucovorin calcium until the methotrexate level is <0.05 micromolar (5 x 10^{-8} M) or 0.01 micromolar (10^{-8} M).

If the 48-hour methotrexate level is >1 micromolar (10^{-6} M) or the 72-hour methotrexate level is >0.2 micromolar (2 x 10^{-7} M): I.V., I.M, Oral: Leucovorin calcium 100 mg/m^2 every 6 hours until the methotrexate level is ≤0.1 micromolar (10^{-7} M). Some clinicians continue leucovorin calcium until the methotrexate level is <0.05 micromolar (5 x 10^{-8} M) or 0.01 micromolar (10^{-8}M).

-Acute lymphoblastic leukemia (ALL):

1-Meningeal leukemia prophylaxis or treatment: Intrathecal: Manufacturer's labeling: 12 mg (maximum 15 mg/dose) every 2 to 7 days; continue for 1 dose beyond CSF cell count normalization. **Note:** Optimal intrathecal chemotherapy dosing should be based on age rather than on body surface area (BSA); CSF volume correlates with age and not to BSA (Bleyer, 1983; Kerr, 2001).

2 -Larson regimen (Larson, 1995; combination therapy):

-Early intensification: Intrathecal: 15 mg day 1 of early intensification phase, repeat in 4 weeks

-CNS prophylaxis/interim maintenance phase:

- Intrathecal: 15 mg day 1, 8, 15, 22, and 29
- Oral: 20 mg/m^2 days 36, 43, 50, 57, and 64

-*Prolonged maintenance:* Oral: 20 mg/m^2 days 1, 8, 15, and 22 every 4 weeks for 24 months
from diagnosis

3-Dose-intensive regimen (Kantarjian, 2000; combination therapy):

- I.V.: 200 mg/m^2 over 2 hours, followed by 800 mg/m^2 over 24 hours beginning day 1, (followed by leucovorin rescue) of even numbered cycles (in combination with cytarabine; alternates with Hyper-CVAD)
- *CNS prophylaxis:* Intrathecal: 12 mg on day 2 of each cycle; duration depends on risk
- *Maintenance:* I.V.: 10 mg/m^2/day for 5 days every month for 2 years (in combination with prednisone, vincristine, and mercaptopurine)

-Breast cancer: I.V.: CMF regimen: 40 mg/m^2 days 1 and 8 every 4 weeks (in combination with cyclophosphamide and fluorouracil) for 6-12 cycles (Bonadonna, 1995; Levine, 1998)

- Choriocarcinoma, chorioadenoma, gestational trophoblastic diseases: 15-30 mg oral or I.M. daily for a 5 day course; may repeat for 3-5 courses (manufacturer's labeling) **or** 100 mg/m^{2}I.V. over 30 minutes followed by 200 mg/m^2 I.V over 12 hours (with leucovorin 24 hours after the start of methotrexate), administer a second course if hCG levels plateau for 3 consecutive weeks (Garrett, 2002)

-Head and neck cancer , advanced: I.V.: 40 mg/m^2 once weekly until disease progression or unacceptable toxicity (Forastiere, 1992; Guardiola, 2004; Stewart, 2009)

-Lymphoma, non-Hodgkin's: I.V.:

-CODOX-M/IVAC regimen (Mead, 2008): Cycles 1 and 3 of CODOX-M (CODOX-M alternates with IVAC)

-Adults ≤65 years: I.V.: 300 mg/m^2 over 1 hour (on day 10) followed by 2700 mg/m^2 over 23 hours (with leucovorin rescue)

-Adults >65 years: I.V.: 100 mg/m^2 over 1 hour (on day 10) followed by 900 mg/m^2 over 23 hours (with leucovorin rescue)

-Hyper-CVAD alternating with high-dose methotrexate/cytarabine regimen: I.V.: 1000 mg/m^2 over 24 hours on day 1 during even courses (2, 4, 6, and 8) of 21-day treatment cycles (Thomas, 2006) **or** 200 mg/m^2 bolus day 1 followed by 800 mg/m^2 over 24 hours during even courses (2, 4, 6, and 8) of 21-day treatment cycles (Khouri, 1998) with leucovorin rescue

-Mycosis fungoides (cutaneous T-cell lymphoma): 5-50 mg once weekly or 15-37.5 mg twice weekly orally or I.M. for early stages (manufacturer's labeling) **or** 25 mg orally once weekly, may increase to 50 mg once weekly (Zackheim, 2003)

-Osteosarcoma: Adults ≤30 years: I.V.: MAP regimen: 12 g/m^2 (maximum dose: 20 g) over 4 hours (followed by leucovorin rescue) for 4 doses during induction (before surgery) at weeks 3, 4, 8, and 9, and for 8 doses during maintenance (after surgery) at weeks 15, 16, 20, 21, 25, 26, 30, and 31 (in combination with doxorubicin and cisplatin) (Meyers, 2005); other combinations, intervals, age ranges, and doses (8-14 g/m^2/dose) have been described (with leucovorin rescue), refer to specific reference for details (Bacci, 2000; Bacci, 2003; Goorin, 2003; Le Deley, 2007; Meyers, 1992; Weiner, 1986; Winkler, 1988)

-Psoriasis: Note: Some experts recommend concomitant folic acid 1-5 mg/day (except the day of methotrexate) to reduce hematologic, gastrointestinal, and hepatic adverse events related to methotrexate.

-Oral: 2.5-5 mg/dose every 12 hours for 3 doses given weekly **or**

-Oral, I.M., SubQ: 10-25 mg/dose given once weekly; titrate to lowest effective dose

Note: An initial test dose of 2.5-5 mg is recommended in patients with risk factors for hematologic toxicity or renal impairment.

-Rheumatoid arthritis: Note: Some experts recommend concomitant folic acid at a dose of least 5 mg/week (except the day of methotrexate) to reduce hematologic, gastrointestinal, and hepatic adverse events related to methotrexate.

-Oral (manufacturer labeling): 7.5 mg once weekly or 2.5 mg every 12 hours for 3 doses/week (dosage exceeding 20 mg/week may cause a higher incidence and severity of adverse events); *alternatively*, 10-15 mg once weekly, increased by 5 mg every 2-4 weeks to a maximum of 20-30 mg once weekly has been recommended by some experts

-I.M., SubQ (unlabeled route): 10-25 mg once weekly (dosage varies, similar to oral) or 15 mg once weekly (Braun, 2008)**.**

Unlabeled uses:

-Bladder cancer (unlabeled use): I.V.:

-Dose-dense MVAC regimen: 30 mg/m^2 day 1 every 2 weeks (in combination with vinblastine, doxorubicin, and cisplatin) (Sternberg, 2001)

-CMV regimen: 30 mg/m^2 days 1 and 8 every 3 weeks for 3 cycles (in combination with cisplatin, vinblastine and leucovorin rescue) (Griffiths, 2011).

-CNS Lymphoma (unlabeled use): I.V.: 8000 mg/m^2 over 4 hours (followed by leucovorin rescue) every 14 days until complete response or a maximum of 8 cycles; if complete response, follow with 2 consolidation cycles at the same dose every 14 days (with leucovorin rescue), followed by 11 maintenance cycles of 8000 mg/m^2 every 28 days with leucovorin rescue (Batchelor, 2003) **or** 2500 mg/m^2 over 2-3 hours every 14 days for 5 doses (in combination with vincristine, procarbazine, intrathecal methotrexate, leucovorin, dexamethasone, and cytarabine) (De Angelis, 2002) **or** 3500 mg/m^2 over 2 hours on day 2 every 2 weeks (in combination with rituximab, vincristine, procarbazine, and leucovorin [with intra-omaya methotrexate 12 mg between days 5 and 12 of each cycle if positive CSF cytology]) for 5 to 7 induction cycles (Shah, 2007)

-Crohn's disease, mild/moderate, corticosteroid-dependent or refractory (unlabeled use):

-Remission induction or reduction of steroid use: I.M., SubQ: 25 mg once weekly

-Remission maintenance: I.M.: 15 mg once weekly

-Dermatomyositis/polymyositis (unlabeled uses):

-Oral: Initial: 7.5-15 mg/week, often adjunctively with high-dose corticosteroid therapy; may increase in weekly 2.5 mg increments to target dose of 10-25 mg/week (**Note:** Administration of folate 5-7 mg/week has been used to reduce side effects)

-I.V., I.M.: Doses of 20-60 mg/week have been employed if failure with oral therapy (doses >50 mg/week may require leucovorin calcium rescue)

-Ectopic pregnancy (unlabeled use): I.M.:

-*Single-dose regimen:* Methotrexate 50 mg/m^2 on day 1; Measure serum hCG levels on days 4 and 7; if needed, repeat dose on day 7

-*Two-dose regimen:* Methotrexate 50 mg/m^2 on day 1; Measure serum hCG levels on day 4 and administer a second dose of methotrexate 50 mg/m^2; Measure serum hCG levels on day 7 and if needed, administer a third dose of 50 mg/m^2

-*Multidose regimen:* Methotrexate 1 mg/kg on day 1; leucovorin calcium 0.1 mg/kg I.M. on day 2; measure serum hCG on day 2; methotrexate 1 mg/kg on day 3; leucovorin calcium 0.1 mg/kg on day 4; measure serum hCG on day 4; continue up to a total of 4 courses based on hCG concentrations

-GVHD (acute) prophylaxis: I.V.: 15 mg/m^2/dose on day 1 and 10 mg/m^2/dose on days 3 and 6 after allogeneic transplant (in combination with cyclosporine and prednisone) **or** 15 mg/m^2/dose on day 1 and 10 mg/m^2/dose on days 3, 6, and 11 after allogeneic transplant (in combination with cyclosporine) **or** 15 mg/m^2/dose on day 1 and 10 mg/m^2/dose on days 3, 6, and 11 after allogeneic transplant (in combination with cyclosporine, followed by leucovorin); may omit day 11 methotrexate (Ruutu, 2013)

-Nonleukemic meningeal cancer (unlabeled uses): Intrathecal: 12 mg/dose twice weekly for 4 weeks, then weekly for 4 weeks, then monthly for 4 doses (Glantz, 1998) **or** 10 mg twice weekly for 4 weeks, then weekly for 1 month, then every 2 weeks for 2 months (Glantz, 1999)**or** 10-15 mg twice weekly for 4 weeks, then once weekly for 4 weeks, then a maintenance regimen of once a month (Chamberlain, 2010).

-Soft tissue sarcoma (desmoid tumors), advanced (unlabeled use): I.V.: 30 mg/m^2 every 7-10 days (dose usually rounded to 50 mg) in combination with vinblastine for 1 year (Azzarelli, 2001)

-Systemic lupus erythematosus, moderate-to-severe (unlabeled use): Oral: Initial: 7.5 mg once weekly; may increase by 2.5 mg increments weekly (maximum: 20 mg once weekly), in combination with prednisone (Fortin, 2008)

-Takayasu arteritis, refractory or relapsing disease (unlabeled use): Oral: Initial dose: 0.3 mg/kg/week (maximum: 15 mg/week), titrated by 2.5 mg increments every 1-2 weeks until reaching a maximum tolerated weekly dose of 25 mg (use in combination with a corticosteroid)

Geriatric

Refer to adult dosing; adjust for renal impairment.

-Breast cancer: Patients >60 years: I.V.: CMF regimen: 30 mg/m^2 days 1 and 8 every 4 weeks (in combination with cyclophosphamide and fluorouracil) for up to 12 cycles (Bonadonna, 1995)

-Meningeal leukemia: Intrathecal: Consider a dose reduction (CSF volume and turnover may decrease with age)

-Non-Hodgkin lymphoma: CODOX-M/IVAC regimen (Mead, 2008): Cycles 1 and 3 of CODOX-M (CODOX-M alternates with IVAC): I.V.: 100 mg over 1 hour (on day 10) followed by 900 mg over 23 hours (with leucovorin rescue)

-Rheumatoid arthritis/psoriasis: Oral: Initial: 5-7.5 mg per week, not to exceed 20 mg per week

Renal Impairment: No dosage adjustment provided in the manufacturer's labeling. The following adjustments have been recommended:

-Aronoff, 2007:

- Cl_{cr} 10-50 mL/minute: Administer 50% of dose
- Cl_{cr} <10 mL/minute: Avoid use
- Hemodialysis: Administer 50% of dose
- Continuous renal replacement therapy (CRRT): Administer 50% of dose.

-Kintzel, 1995:

- Cl_{cr} 46-60 mL/minute: Administer 65% of normal dose
- Cl_{cr} 31-45 mL/minute: Administer 50% of normal dose
- Cl_{cr} <30 mL/minute: Avoid use
- Hemodialysis patients with cancer (Janus, 2010): Administer 25% of dose after hemodialysis; monitor closely for toxicity

-High-dose methotrexate, dose-intensive regimen for ALL (200 mg/m^2 over 2 hours, followed by 800 mg/m^2 over 24 hours with leucovorin rescue (Kantarjian, 2000):

- Serum creatinine <1.5 mg/dL: No dosage adjustment necessary
- Serum creatinine 1.5-2 mg/dL: Administer 75% of dose
- Serum creatinine >2 mg/dL: Administer 50% of dose

Hepatic Impairment:

No dosage adjustment provided in the manufacturer's labeling; use with caution in patients with impaired hepatic function or pre-existing hepatic dysfunction. The following adjustments have been recommended (Floyd, 2006):

- Bilirubin 3.1-5 mg/dL **or** transaminases >3 times ULN: Administer 75% of dose
- Bilirubin >5 mg/dL: Avoid use

Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

Dosing: Adjustment for Toxicity

-Nonhematologic toxicity: Diarrhea, stomatitis, or vomiting which may lead to dehydration: Discontinue until recovery

-Hematologic toxicity:

-Psoriasis, rheumatoid arthritis: Significant blood count decrease: Discontinue immediately.

-Oncologic uses: Profound granulocytopenia and fever: Evaluate immediately; consider broad-spectrum parenteral antimicrobial coverage

Common side effect :

>10%:

Central nervous system (with intrathecal administration or very high-dose therapy):

Arachnoiditis: Acute reaction manifested as severe headache, nuchal rigidity, vomiting, and fever; may be alleviated by reducing the dose

Subacute toxicity: 10% of patients treated with 12-15 mg of intrathecal methotrexate may develop this in the second or third week of therapy; consists of motor paralysis of extremities, cranial nerve palsy, seizure, or coma. This has also been seen in pediatric cases receiving very high-dose I.V. methotrexate.

Demyelinating encephalopathy: Seen months or years after receiving methotrexate; usually in association with cranial irradiation or other systemic chemotherapy

Dermatologic: Reddening of skin

Endocrine & metabolic: Hyperuricemia, oligospermia

Gastrointestinal: Ulcerative stomatitis, glossitis, gingivitis, nausea, vomiting, diarrhea, intestinal perforation, mucositis (dose dependent; appears in 3-7 days after therapy, resolving within 2 weeks)

Hematologic: Leukopenia, myelosuppression (nadir: 7-10 days), thrombocytopenia

Renal: Renal failure, azotemia, nephropathy

Respiratory: Pharyngitis

Miscellaneous: Immunosuppression

1% to 10%:

Cardiovascular: Vasculitis

Central nervous system: Dizziness, malaise, fever, chills

Dermatologic: Alopecia, rash, photosensitivity, depigmentation or hyperpigmentation of skin, pruritus, dermatitis

Endocrine & metabolic: Diabetes

Genitourinary: Cystitis

Hematologic: Hemorrhage

Hepatic: Cirrhosis (chronic therapy), liver function tests increased (chronic therapy), portal fibrosis (chronic therapy)

Neuromuscular & skeletal: Arthralgia

Ocular: Blurred vision

Pregnancy category: X