Systemic Drug Therapy in Dermatology - II

Clinical vignette

- A 45 year old male presents with well-defined erythematous papules and plaques, which are surmounted with large, silvery loose scales. There is also associated joint pain

- Provisional diagnosis

- Psoriasis with psoriatic arthritis

- The treating physician plans an immunosuppressive (e.g. methotrexate) and with other routine investigations (e.g. CBCs, ESR, BUN, creatinine etc.), orders serum virological markers (for HBV, HCV, HIV)
- In a tropical country like India, which other infection/ inv. is also routinely indicated before treatment

- Tuberculosis
- CXR

Methotrexate (MTX)

- An antimetabolite - Used as a chemotherapeutic agent since the early 1950s
- Immunosuppressive and anti-inflammatory effects
- Used therapeutically in a variety of rheumatological, gastrointestinal, neurological and *dermatological* inflammatory disorders

Uses

- Severe psoriasis with/without arthritis
- Off-label (often as a steroid-sparing agent) in immunobullous disorders (pemphigus, bullous pemphigoid, cicatricial pemphigoid and epidermolysis bullosa acquisita),
- Connective tissue diseases (dermatomyositis, lupus erythematosus and scleroderma),
- Vasculitides
- Neutrophilic dermatoses (pyoderma gangrenosum and Sweet syndrome)
- Other inflammatory (such as atopic eczema, sarcoidosis, cutaneous Crohn disease and chronic idiopathic urticaria) and proliferative (mycosis fungoides, Sézary syndrome, pityriasis lichenoides and pityriasis rubra pilaris) disorders

Efficacy in psoriasis

- In treatment of psoriasis and psoriatic arthritis - MTX is considered the "*gold standard*"
- Based on several studies - Approximately 45% of patients see a 75% improvement in their Psoriasis Area and Severity Index (PASI) score
- Takes - 4 to 8 weeks to see a response to changes in MTX dosage

Doses

- In dermatological usage, MTX is usually taken orally in weekly (rather than daily) doses,
- Also - Intramuscular, intravenous, subcutaneous
- Usual weekly dose – 7.5-20 mg

Mechanisms of action

- A structural analogue of folic acid
- MTX - blocks the metabolism of folic acid through competitive inhibition of dihydrofolate reductase (DHFR)
- DHFR catalyses the conversion of DHF to tetrahydrofolate (THF), a single-carbon transfer source essential to the generation of purine & pyrimidine nucleotides → Therefore for nucleic acid and protein synthesis

Risks, Precautions, Common ADRs

Risks and Precautions With Methotrexate Use

- Absolute contraindications
  - Pregnancy (category X)
  - Lactation
  - Significant anemia, leukopenia, or thrombocytopenia
- Relative contraindications
  - Renal dysfunction (dose may be reduced)
  - Hematologic disease (dose may be reduced)
  - Hepatic disease or hepatic dysfunction
  - Unreliable patient
  - Excessive alcohol consumption
  - Diabetes mellitus and/or obesity
  - Active infection and/or potential reactivation of infection (tuberculosis)
  - HIV infection
  - Man or woman contemplating impending conception
- Common adverse effects
  - GI distress (minimized with folate supplementation)
  - Myelosuppression (acute)
  - Toxic hepatitis
  - Liver fibrosis/cirrhosis (chronic)

Pre-treatment screening

Box 19.1 Suggested pre-treatment checklist for cytotoxic and immunosuppressive therapy

- Patient information leaflet
- Risk counselling
  - Infection
  - Bone marrow suppression
  - Skin malignancy
  - Lymphoma
  - Conception-related hazards
- Contraception
- Cervical screening concordance (pre-treatment gynaecological review if there is a history of dysplastic change)
- Sun protection measures
- General skin examination for dysplastic and neoplastic lesions
- Blood tests
  - Full blood count
  - Urea and electrolytes
  - Liver function tests
  - Hepatitis B and C serology
  - HIV serology (if there are positive risk factors)
  - Varicella zoster virus serology (if chickenpox history is uncertain)
- Vaccinations
  - Pneumococcal vaccination
  - Seasonal influenza vaccination
  - Hepatitis B (if seronegative)
  - Varicella zoster virus vaccination (if seronegative – several weeks prior to commencing treatment as vaccine is live)
  - Consider travel-related vaccinations

Ongoing monitoring

Laboratory Monitoring for Methotrexate[a]

CBC, platelets	7-14 d after drug initiation, then every 2-4 wk for the first few months, then every 1-3 mo, depending on leukocyte count and patient stability
Renal function studies	Serum BUN and Cr levels at 1- to 2-mo intervals: GFR for patients at risk for decreased renal function
Liver chemistries: AST, ALT alkaline phosphatase, serum albumin	Every 4-8 wk (more frequent liver chemistry monitoring in lieu of an initial liver biopsy for patients with hepatic risk factors)
Pregnancy test	Women of childbearing potential

Liver biopsy

- The gold standard to assess MTX-induced liver fibrosis - Percutaneous needle biopsy
- Patients without risk factors for liver injury - Current recommendations suggest consideration of liver biopsy after 3.5 to 4 g total cumulative dosage.
- For patients with risk factors - For MTX-induced liver injury, a delayed baseline liver biopsy should be considered (after 2-6 months of use, when it is apparent the medication is efficacious, well tolerated, and likely to be continued) and again at a cumulative dose of 1.0 to 1.5 g

Folate Supplementation

- Daily supplementation with 1 to 5 mg of folate - Reduced adverse effects and toxicities without compromising the efficacy of MTX
- Nausea, vomiting, diarrhea, alopecia, stomatitis and oral ulceration, elevated transaminases, and mild myelosuppression – May be prevented
- Pneumonitis & moderate to severe myelosuppression - Not mitigated by folate supplementation

Overdose

- MTX overdose – Must be treated promptly (within 24-36 hours after overdose) with folinic acid (leucovorin)
- Folinic acid is metabolized *in vivo* to tetrahydrofolate in the absence of dihydrofolate reductase - Provides an alternative supply of DNA and RNA precursors
- An oral dose of 10 mg/m2, or 15 to 25 mg every 6 hours for 6 to 10 doses should be given on first suspicion of MTX overdose without delay for a serum assay
- If serum assay is available, oral or parenteral doses may be continued every 6 hours until the serum concentration of MTX falls to less than 10^{-8} M

Drug Interactions

Box 19.9 Methotrexate: drug–drug interactions

The interaction of MTX with other drugs can occur via a number of mechanisms [29].

- Reduced absorption from gut: *digoxin* (absorption reduced by MTX), *neomycin*
- Displacement from plasma proteins: *NSAIDs* (*aspirin*, *diclofenac*, *ibuprofen*, *indometacin*, *ketoprofen*, *meloxicam* and *naproxen*), *sulphonamides*
- Added antifolate effect: *nitrous oxide*, *trimethoprim*, *sulphonamides*, *dapsone*, *phenytoin*, *pyrimethamine*
- Diminished renal excretion: *ciprofloxacin*, *NSAIDs*, *omeprazole*, *penicillins*, *probenecid*, *sulphonamides*
- Increased renal excretion: *acetazolamide*
- Cumulative toxicity: *tetracyclines*, *acitretin*, *clozapine*, *ciclosporin*, *cisplatin*, *leflunomide*, *alcohol*
- Other: *theophylline* (plasma levels increased by MTX)

Azathioprine

- A potent immunosuppressive, anti-inflammatory and antiproliferative drug
- To prevent graft rejection and to treat haematological malignancies and a variety of rheumatological, gastrointestinal, neurological and *dermatological* inflammatory disorders

Uses

- Pemphigus and pemphigoid
- Often used as an adjunct to other immunosuppressive agents such as prednisolone and *may exert a steroid-sparing* effect
- Systemic lupus erythematosus and dermatomyositis
- Atopic eczema
- Chronic actinic dermatitis
- Also for use in - Lichen planus, contact dermatitis, polymorphic light eruption, leukocytoclastic vasculitis, pyoderma gangrenosum, Behçet disease and chronic cutaneous lupus erythematosus

MoA

- Azathioprine is a prodrug that is metabolized to 6-mercaptopurine (6-MP) and acts as an immunosuppressant/ anti-inflammatory
- Has better availability when given by mouth than 6-MP
- 6-MP is further anabolized via hypoxanthineguanine phosphoribosyl transferase (HGPRT) → ultimately to a purine analog, 6-thioguanine (6-TG) → which inhibits RNA and DNA synthesis and repair →immunosuppression

CIs & Common ADRS

Risks and Precautions With Azathioprine Use

- Absolute contraindications
  - Hypersensitivity to azathioprine
  - Active or ongoing infection
- Relative contraindications
  - Pregnancy/lactation (category D, but myelosuppression of fetus/infant common—avoid)
  - Allopurinol use (dose must be reduced by 75%)
  - Prior lymphoproliferative disease or prior use of alkylating agents
- Common adverse effects
  - GI distress (minimized by administration with food)
  - Myelosuppression
  - Possible increased risk of lymphoproliferative disease or skin cancer
  - Possible opportunistic infections

Doses

- Usual dose: 1-2.5 mg/kg
- Azathioprine can be initiated as monotherapy
- Initially combined with prednisone is often used in steroid-responsive bullous disorders

Cyclophosphamide

- Cyclophosphamide is an alkylating agent and acts primarily by crosslinking DNA - A classic cell cycle-nonspecific cytotoxic drug
- In oncology - Used as an antineoplastic agent
- In dermatology - Used as an immunosuppressive and steroid-sparing agent particularly for autoimmune blistering disorders and systemic vasculitis

Indications

- In dermatology, used in only the *most* serious diseases
- In particular - Pemphigus vulgaris - In combination with steroids - Evidence supports its steroid-sparing benefits
- Cyclophosphamide - Also used for the treatment of mucous membrane pemphigoid
- Other diseases that may respond - Pyoderma gangrenosum, necrobiotic xanthogranuloma, cutaneous amyloidosis, lichen myxedematosus, giant cell reticulohistiocytoma, primary cutaneous diffuse large B-cell lymphoma and mycosis fungoides

Doses

- Oral doses - Typically 1 to 3 mg/kg/d either divided or as a single morning dose

ADRs

Risks and Precautions With Cyclophosphamide Use

- Absolute contraindications
  - Hypersensitivity to cyclophosphamide (can cross-react with chlorambucil)
- Relative contraindications
  - Pregnancy/lactation (category D; fetal loss common)
  - History of transitional cell carcinoma of the bladder
  - Depressed bone marrow function
  - Impaired hepatic or renal function
- Common adverse effects
  - GI distress (minimized with antiemetic medications)
  - Myelosuppression (often dose limiting)
  - Hemorrhagic cystitis due to elimination of toxic metabolites (minimized with mesna)
  - Carcinogenicity (transitional cell carcinoma of bladder, lymphoproliferative disease)
  - Reproductive consequences (amenorrhea, azoospermia, gonadal failure)

Mycophenolate mofetil

- Mycophenolate mofetil (MMF) - potent immunosuppressant
- Prodrug of mycophenolic acid (MPA) - Used primarily to prevent solid-organ graft rejection

Dermatological uses

- MMF has a predictably beneficial effect in the treatment of immunobullous disorders (in particular pemphigus and pemphigoid)
- A less consistent effect in psoriasis, atopic eczema, connective tissue disorders and vasculitides

Dose

- Twice-daily dosing
- Starting dose for dermatological indications - 250 mg BD first week
- Until a maximum of 1.5 g twice daily is reached
- Dosage should be tailored to individual tolerance
- The clinical response is slow

Ciclosporin

- Ciclosporin is a highly effective and rapidly acting potent inhibitor of T-cell function
- Central importance in the management of severe inflammatory skin disease, particularly psoriasis

Indications

- Cicloporin - psoriasis (plaque type) and atopic eczema
- Common off-label uses include chronic urticaria, pyoderma gangrenosum, hand eczema and palmoplantar pustulosis

ADRs

- MC - Hypertension, nephrotoxicity, hyperlipidaemia, myalgia and headache
- Others include gingival hyperplasia, fatigue, gastrointestinal disturbances,
- tremor and paraesthesiae in the hands and feet
- A variety of metabolic abnormalities (hyperbilirubinaemia, hypercalcaemia,
- hypomagnesaemia, hyperuricaemia)
- Most are dose related and respond rapidly to dose reduction/ treatment cessation
- Longer term use carries significant, predictable risk, particularly of nephrotoxicity, and is generally not recommended

Doses

- Start - In the lower dose range (2.5 mg/kg/day), escalating to higher doses (up to 5 mg/kg/day) after a month of therapy in the event of a poor response
- If disease is acute, severe and/or unstable -5 mg/kg/day
- The lowest possible therapeutic dose should be used

- Ciclosporin remains an extremely useful, predictably effective and generally well-tolerated drug for short-term use
- Long-term use is complicated by nephrotoxicity
- Potent immunosuppression.

Thalidomide

- Hypnosedative, immunomodulatory, and neural/vascular tissue effects
- Initially removed from the market because of severe teratogenic effects (phocomelia) in 1961

Indications

- Thalidomide - Later found to be effective in treating erythema nodosum leprosum
- Off-label use treating dermatoses including AIDS-related Kaposi sarcoma, pyoderma gangrenosum, bullous pemphigoid, prurigo nodularis, uremic pruritus

Dose and regimens

- The dose range for dermatological conditions is 50–300 mg/day, taken as a single dose at bedtime to reduce the impact of sedation

Systemic retinoids

- The synthetic retinoids are a class of organic molecules derived from and with similar biological activity to the naturally occurring vitamin A group of retinoids, which includes retinol, retinal and retinoic acid

Indications

- Isotretinoin is licensed for the treatment of severe acne resistant to adequate courses of standard therapy, although *off-label* it has been used in rosacea, hidradenitis suppurativa and dissecting cellulitis of the scalp
- Alitretinoin has a product license to treat severe chronic hand eczema
- Also been approved by FDA for the topical treatment of the cutaneous lesions of Kaposi sarcoma

- Acitretin - severe psoriasis, resistant to standard therapies, palmoplantar pustulosis, inherited ichthyoses and Darier disease
- Bexarotene is indicated for the treatment of the cutaneous manifestations of advanced cutaneous T-cell lymphoma

- Retinoids have also been used off-license to treat pityriasis rubra pilaris, lupus erythematosus and lichen planus

Doses

Dosing Regimens of Retinoids in Major Indications

DRUG	INDICATION	INITIALLY (mg/kg/day)	SUSTAINED (mg/kg/day)	LENGTH OF THERAPY (months)
Isotretinoin	Acne	0.3–0.5	0.5–1.0	4–6
Acitretin	Psoriasis	0.2–0.5	0.3–0.8	>3
	DOK[a]	0.3–0.6	0.5–1.0	>3
Alitretinoin	Hand eczema	10–30[b]	10–30[b]	>6
Bexarotene	CTCL	4–8	2–4 (8)	>2

ADRs

Adverse Effects of Systemic Retinoids: A Summary

	ISOTRETINOIN	ALITRETINOIN	ACITRETIN	BEXAROTENE
Teratogenicity	+	+	+	+
Mucocutaneous	+	+	+	+
Ocular	++	+	+	+
Alopecia	(+)	+	+	+
Headache	+	++	+	+
Musculoskeletal	++	+	+	+
Hepatotoxicity	(+)	(+)	+	+
Neutropenia	–	–	–	+
Hyperlipidemia	++	+	+	++
Hypothyroidism	–	+	–	+

Box 19.11 Systemic retinoids: drug–drug interactions [41]

- Tetracyclines increase the risk of benign intracranial hypertension
- Alcohol induces acitretin re-esterification to etretinate, very significantly increasing its effective half-life
- Effects of coumarin anticoagulants and simvastatin possibly reduced by acitretin
- Carbamazepine plasma concentrations possibly reduced by isotretinoin
- Ketoconazole increases plasma concentrations of alitretinoin
- Possible methotrexate toxicity with acitretin
- Gemfibrozil increase bexarotene plasma levels
- Concomitant vitamin A may induce hypervitaminosis A

Pre-treatment screening

- Women of childbearing potential - explicit counselling on the teratogenicity of retinoids
- Either adopt birth control measures or abstain from coitus
- Pregnancy should be excluded prior to commencing retinoid therapy
- Pregnancy should be avoided for the duration of therapy and for an appropriate time thereafter (1 month for isotretinoin, alitretinoin and bexarotene, and 2 years for acitretin)
- The recommendations regarding isotretinoin, which can be adapted of the other retinoids, suggest that women deemed at risk of conceiving should be recruited into the isotretinoin pregnancy prevention plan (iPLEDGE in the USA

Monitoring

- Reasonable follow-up - Monthly clinical evaluation
- Blood tests (liver function tests and fasting lipid profile, with occasional renal function tests and full blood count) for 3–6 months, then 3-monthly reviews with blood tests
- Thyroid function should be monitored in patients receiving alitretinoin and bexarotene

THANK YOU