The safety and handling of low dose methotrexate: myths and realities

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Oral low dose methotrexate (LDM) is used in a wide variety of rheumatic, gastroenterological, neurological and dermatological conditions. These include rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, and inflammatory bowel disease. In this context, LDM is defined as 2.5–30 mg once per week, it is usually given with supplementary folic acid/folate that has been shown to reduce oral and gastrointestinal side effects and reduces the incidence of abnormal liver tests.1–3

The recommended dose of folic acid is at least 5 mg per week in any dosing regimen.4 In contrast, high dose methotrexate used in a haematological/cancer setting may be dosed in grams, and therapy with leuvocorin/folinic acid is often required to rescue from bone marrow failure. Unfortunately, the precautions appropriate for haematological dosing are sometimes applied to LDM. LDM should not be considered chemotherapy.

Misinformation abounds on the part of both patients and health professionals. This results in a large amount of unnecessary anxiety for patients, pharmacists and nursing staff as well as wasted time and costs associated with unnecessary barrier protection. Most worrying is the lost opportunity for prompt disease control. In the past decade, ‘the window of opportunity’ that exists in autoimmune inflammatory arthritis such as RA has been clearly identified.5 Patients with uncontrolled RA or another inflammatory disease can decline treatment with the anchor disease modifying anti-rheumatic drug (DMARD) methotrexate because of concerns founded on the inappropriate and ill-informed advice. This is often given by healthcare practitioners based on high dose haematological/cancer use and unfortunately this is highly likely to be associated with poor disease control or treatment for the patient.6

The action of low dose methotrexate
Initially, the action of LDM was thought to be mediated through reduced purine and pyrimidine synthesis and thereby reduced proliferation of lymphocytes and other immune cells that potentiate inflammation.7 This has been observed transiently for 24 hours after dosing in one study.8 The observation that neither folic acid nor folinic acid counters the effect of LDM argues strongly that this is not the mechanism. It is beyond the scope of this article to discuss the detailed experimental data on LDM action, but it is clear there are likely to be a number of different actions, including effects on intra-cellular glutathione levels, increased adenosine production or reduced pro-inflammatory transmethylation products.7 There is no evidence that methotrexate at low doses exerts its effects by cellular cytotoxicity, as it does when used in high doses in the field of oncology.

Benefits
The benefits of LDM are multiple across many diseases. In RA, it is the cornerstone of DMARD therapy recognised by international guidelines in both North America and Europe.9,12 It is used first line and recommended to be commenced at time of diagnosis. LDM reduces disease activity and joint damage, and is thought to also prolong life through its anti-inflammatory effect protecting from cardiovascular disease.11 A prospective six-year study reported a 70% reduction in cardiovascular death in those taking LDM compared to non-users.16 For almost all RA patients, LDM is the first choice of disease modifying agent with significant excess benefit over potential risk of adverse event.

Potential adverse effects
Trial data has shown that with use of 25 mg oral methotrexate, 14% will develop oral ulcers, 12% diarrhea and 29% nausea.10 These side effects may be alleviated by use of additional oral folic acid, folinic acid or the use of sub-cutaneous dosing. While elevations in liver tests are common (22% in one study),16 the risks of clinically significant white count reduction, liver test abnormality and pulmonary complications are low. Only two of 248 patients had their LDM discontinued due to laboratory abnormalities in a longitudinal study covering 1,007 person-years, most patients discontinued LDM for clinical reasons not laboratory findings.17

If there is difficulty tolerating oral methotrexate a number of approaches can be trialed including: reducing the methotrexate dose, initiating or increasing folinic acid / folic acid supplementation, switching from oral to sub-cutaneous dosing and/or dividing the methotrexate dose over 12 hours. The current Australian Pharmaceutical Benefits Scheme (PBS) toxicity descriptors state that a minimum of three doses of methotrexate should have been trialed before this important treatment is withdrawn.18 In a recent study 75% of patients who were intolerant to oral administration tolerated the switch to subcutaneous dosing.19

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Low dose methotrexate and NSAIDs

Whilst reference books report that there is a drug interaction between LDM and non-steroidal anti-inflammatory agents (NSAIDs), this is not a clinically significant interaction. Case reports exist describing the purported interaction, but the specific details of the interactions described in the reports are far from clear.20 There are also many thousands of patients all over the world who regularly use NSAIDs with their methotrexate without developing adverse effects. In vitro evidence also supports the premise that the interaction is not clinically significant.21

The appropriateness of low dose methotrexate precautions

Many hospitals and other healthcare institutions mandate that LDM be handled in the same way as high dose methotrexate. A recent Australian study exposed healthy volunteers to an entire dose of 25 mg of LDM on their skin for 30 minutes.22 The minimum reliable assayed serum methotrexate level was not detected at any time, in any of the six participants. Urine methotrexate was also extremely low. This extreme 30 minute dermal exposure experiment demonstrates that the precautions taken when handling low dose methotrexate are excessive. No special precautions are required when handing LDM tablets. They can be treated like other tablets by nurses and pharmacy staff.

Precautions such as barrier nursing with masks, gowns and double gloving, or using special gloves is excessive based on the evidence. There is no contraindication to mixing LDM tablets with the patients other medications in a blister pack, for example, because the patient is taking all of the tablets. Importantly, separating LDM tablets from the patients other tablets may also impact negatively on adherence because it is a separate weekly thing to remember to take in addition to blister packs medications. Additional precautions such as not kissing babies, flushing the toilet multiple times and avoiding contact with any person because of the perceived risk of methotrexate exposure to a third party are not justified by the evidence. Concentrations in the saliva and sweat of patients bear little relation to serum levels and were 0.55–2.3% when a oncology dose of 0.5–0.6 g/m²
was used.26 Even if a particle of saliva from a patient taking LDM were to land on the skin of another person the recent Australian skin exposure study demonstrates that this poses no risk.

Advice to patients

As rheumatologists, we hear from our patients that they have been advised by ‘well-meaning’ friends and family, and by some misinformed health professionals that LDM is a dangerous oncology ‘cancer’ or chemotherapy drug with drastic side effects and life threatening complications (see Box 1). As with any medication, there are risks and benefits. When deciding to prescribe LDM, these are taken into account, and the risk-benefit equation is discussed with the individual patient. When that patient subsequently hears different information outlining a set of apparently more sinister risks, albeit from well meaning advisors, the patient’s chance of optimal care is potentially compromised. This situation benefits no one. While some patients will return to discuss this with the prescriber, too many will, through ill-informed fear, elect to leave their disease untreated.

Summary

The evidence that methotrexate, when used in low dose for autoimmune and other inflammatory diseases, is a cytotoxic agent and hence in need of oncology type precautions is non-existent. Patients on LDM should not be treated with the same precautions as patients receiving high dose methotrexate. The risks and benefits of LDM are different to high dose methotrexate and any advice given to patients taking LDM needs to reflect that.

As patients easily access multiple information sources on the internet, some reliable and some dangerous, it is critical that all members of the multidisciplinary healthcare team convey the same scientifically correct message. LDM should not be considered chemotherapy. The risks and benefits of LDM should be portrayed appropriately so that each patient can make an informed decision about therapy in conjunction with their prescriber. It is hoped this article goes some way to promoting that ideal.

References