Methotrexate and Pralatrexate

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KEYWORDS

• Methotrexate • Pralatrexate • Dihydrofolate reductase • Folate • Folic acid • Purine synthesis • S phase • Apoptosis

KEY POINTS

- Methotrexate (MTX) and pralatrexate (PDX) are competitive inhibitors of folate metabolism that block dihydrofolate reductase, thereby preventing thymidylate and purine synthesis and resulting in cell cycle arrest in the S phase.
- MTX and other folate inhibitors also reduce cellular levels of S-adenosylmethionine, the principal methyl donor for methyltransferases, thereby inhibiting DNA methylation.
- In CTCL, this derepresses tumor suppressor genes such as the death receptor, Fas (CD95), thereby enhancing apoptosis.
- These properties make folate antagonists useful for the treatment of lymphomas, either as single agents or in combination with other therapies that enhance or complement their effects.

INTRODUCTION

Methotrexate (MTX) is a well-known antimetabolite that blocks the action of dihydrofolate reductase, thereby inhibiting the metabolism of folic acid. It has been used widely since the 1950s to treat a variety of neoplastic and inflammatory diseases. Recently, a more potent analog, pralatrexate (PDX), has been developed and approved by the Food and Drug Administration (FDA) for the treatment of peripheral T-cell lymphomas (PTCLs). This article discusses some emerging concepts relevant to the optimal use of folate antagonists and reviews these drugs in regard to the therapy for cutaneous T-cell lymphomas (CTCLs), including clinical indications, mechanism of action, pharmacokinetics, dosing regimens, response rates, and adverse effects. According to convention, MTX will be used as the abbreviation for methotrexate. In keeping with prior publications, pralatrexate will be abbreviated as PDX, a designation derived from its alternative name: 10-propargyl-10-deazaaminopterin.[1]

EMERGING CONCEPTS RELEVANT TO THE OPTIMAL USE OF FOLATE ANTAGONISTS

The Role of Folate Antagonists in the Epigenetic Regulation of Gene Expression

The products of at least 5 tumor suppressor genes generally known to be silenced by promoter methylation have been reported to be deficient in mycosis fungoides (MF) and Sézary syndrome (SS), FAS/CD95, FAS-ligand, p16, p21, and protein phosphatase 4 regulatory subunit-1 (PP4R1).[2–11] These and other genes are also known to be silenced by promoter methylation in many other cancers (eg, TRAIL-R1, TRAIL-R2, p16, p21, hMLH1, MGMT, and RASSF1A).[12,13] These findings suggest that demethylating agents

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could benefit MF/SS patients by derepressing silenced tumor suppressor genes. Although FDA-approved for use in other diseases, traditional demethylating agents such as 5-azacytidine and decitabine have a toxicity profile that discourages their use for the treatment of chronic cutaneous lymphomas such as MF/SS. One of the most exciting aspects of folate antagonists is the recent realization that, in addition to their well-established role as S phase cell cycle inhibitors, they can also act as DNA methylation inhibitors.[2,14] Most of the relevant experiments have been performed using MTX; however, all related folate antagonists should share the same basic properties (see later discussion).

The Importance of Combination Therapy for Cancer

Inhibition of DNA methylation constitutes a novel mechanism of action and rationale for the use of MTX and related compounds in the management of cutaneous lymphomas. It also provides a new justification for their use in combination with other treatments that produce effects complementary to those of folate antagonists. The advantages of combination therapy relative to monotherapy for cancer treatment have been calculated recently by Bozic and colleagues.[15] In brief, they used mathematical modeling to show that by the time a tumor reaches a few millimeters in diameter it is likely to harbor hundreds to thousands of mutant cells that are resistant to any particular monotherapy. This typically results in short-term clinical benefit followed by treatment failure because resistant mutant tumor clones proliferate in response to the selection pressures of monotherapy. In contrast, dual therapy results in long-term disease control in most cases, if there are no mutations in a single cell that cause cross-resistance to both agents. The chances of cross-resistance are diminished if the 2 agents target different pathways. For patients with large disease burden in which the number of resistant mutants is greater, triple therapy is needed. The mathematical models also showed that simultaneous therapy with 2 agents is much more effective than when they are used as sequential therapies.

The implications of these mathematical models are relevant to folate antagonists because these drugs can be used in combination with other treatments that have different mechanisms of action and affect multiple cellular pathways. **Table 1** summarizes examples of MTX in combination with other modalities. Using this combination therapy approach, the likelihood of a favorable therapeutic outcome can be enhanced.

TREATMENT

Indications

MTX and PDX have been used to treat a wide variety of cancers. Among the cutaneous lymphomas, MTX has been used primarily to treat MF/SS and primary cutaneous CD30+ lymphoproliferative disorders (LPDs) such as lymphomatoid papulosis (LyP) and anaplastic large cell lymphoma (cALCL). PDX is FDA-approved for refractory or relapsed PTCLs. Among the cutaneous lymphomas, it has proven efficacy for advanced stages of MF/SS, including MF with large cell transformation (LCT).[16,17] It has also been used to treat other rarer forms of primary CTCLs.[18–20] Folate antagonists have not been used widely to treat cutaneous B-cell lymphomas. In fact, MTX has been associated with the development of cutaneous B-cell LPDs (sometimes related to Epstein-Barr virus), many of which regress when MTX is reduced or discontinued.[21,22]

Mechanism of Action

MTX and PDX are folic acid analogues that block cell division in the S phase.[23,24] They are competitive inhibitors of dihydrofolate reductase with an affinity for this enzyme that is several logs greater than that of its natural substrate, folate. Dihydrofolate reductase converts dihydrofolate to tetrahydrofolate, which is required for synthesis of thymidylate and purine nucleotides involved in DNA and RNA synthesis. It also inhibits the folate-dependent enzymes of purine and thymidylate synthesis such as glycinamide ribonucleotide transformylase, aminoimido-caboxyamido-ribonucleotide transformylase, and thymidylate synthase. MTX also inhibits methionine synthase, thereby reducing S-adenosyl methionine (SAM) levels. Because SAM is the principal methyl donor for DNA methyltransferases (DNMTs),[25,26] the authors propose that MTX can act as a demethylating agent by depleting DNMTs of their SAM methyl donor supply. The mechanism underlying this effect is illustrated in **Fig. 1**. Recently, the authors reported in vitro and ex vivo evidence that MTX acts as a demethylating agent for the promoter of the FAS/CD95 death receptor by blocking the synthesis of SAM.[14] When CTCL cell lines and freshly isolated leukemic CTCL cells were treated with MTX, it resulted in decreased SAM levels, decreased FAS promoter methylation, and increased FAS protein expression. This enhanced FAS expression was accompanied by a major increase in sensitivity to FAS pathway apoptosis, especially for leukemic cells. In strong support of the authors' hypothesis regarding MTX's mechanism of action, experiments using CTCL lines with high baseline FAS

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