

Tetrahydrofolate or *N*5-formyltetrahydrofolate (leucovorin) can bypass this block and rescue cells from methotrexate, which is retained in cells by polyglutamylation. Methotrexate is transported into cells by a membrane carrier, and high concentrations of drug can bypass this carrier and allow diffusion of drug directly into cells. These properties have suggested the design of “high-dose” methotrexate regimens with leucovorin rescue of normal marrow and mucosa as part of curative approaches to osteosarcoma in the adjuvant setting and hematopoietic neoplasms of children and adults. Methotrexate is cleared by the kidney via both glomerular filtration and tubular secretion, and toxicity is augmented by renal dysfunction and drugs such as salicylates, probenecid, and nonsteroidal anti-inflammatory agents that undergo tubular secretion. With normal renal function, 15 mg/m² leucovorin will rescue 10⁻⁸–10⁻⁶ M methotrexate in 3–4 doses. However, with decreased creatinine clearance, doses of 50–100 mg/m² are continued until methotrexate levels are <5 × 10⁻⁸ M. In addition to bone marrow suppression and mucosal irritation, methotrexate can cause renal failure itself at high doses owing to crystallization in renal tubules; therefore, high-dose regimens require alkalinization of urine with increased flow by hydration. Methotrexate can be sequestered in third-space collections and diffuse back into the general circulation, causing prolonged myelosuppression. Less frequent adverse effects include reversible increases in transaminases and hypersensitivity-like pulmonary syndrome. Chronic low-dose methotrexate can cause hepatic fibrosis. When administered to the intrathecal space, methotrexate can cause chemical arachnoiditis and CNS dysfunction.

Pemetrexed is a folate-directed antimetabolite that inhibits the activity of several enzymes, including thymidylate synthetase (TS), dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase. To avoid toxicity to normal tissues, pemetrexed is given with low-dose folate and vitamin B₁₂ supplementation. Pemetrexed has notable activity against certain lung cancers and, in combination with cisplatin, also against mesotheliomas.