The fact that any type of chemotherapy that results in DNA damage may cause cancer (even if such cancer has not been observed) has prompted a warning in the package insert for methotrexate.

The package insert for low-dose methotrexate mentions cancer (neoplasms), but does not expressly assert that cancer is a risk: "No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate" (139).

Please also note that etoposide, which is used to treat various cancers, such as ovarian cancer, can cause leukemia (140).

b. Paradox with growth factors for cancer

A paradox can occur where a growth factor is administered as part of anti-cancer therapy.

Women receiving chemotherapy for breast cancer have received a small molecule drug in combination with a biological (growth factor). Thus, in addition to small molecule drugs, cancer patients may receive a growth factor, such as granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) (141).

The desired effect of the administered growth factor is prevention of neutropenia (142). The prophylactic administration of the growth factor reduces the need for chemotherapy dose reductions and delays that may limit chemotherapy dose intensity. By reducing the need for dose reductions, the administered growth factor increases the potential for prolonged disease-free and overall survival in the curative setting (143).

Neutropenia is the primary dose-limiting toxicity in patients treated with chemotherapy that suppresses the formation of white blood cells (myelosuppressive chemotherapy), leading to morbidity and mortality, and disrupting treatment with curative regimens. The use of granulocyte colony-stimulating factors (G-CSFs) as primary

[139] Bedford Laboratories, Bedford, OH. Package Insert. Methotrexate Injection USP. April 2005.

[140] Dunton CJ. Management of treatment-related toxicity in advanced ovarian cancer. *The Oncologist*. 2002;7(suppl 5):11–19.

[141] Hershman D, Neugut AI, Jacobson JS, et al. Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy. J. Natl. Cancer Inst. 2007; 99:196–205.

[142] Rader M. Granulocyte colony-stimulating factor use in patients with chemotherapy-induced neutropenia: clinical and economic benefits. *Oncology (Williston Park)*. 2006;20(5 suppl 4):16–21.

[143] Lyman GH. Guidelines of the National Comprehensive Cancer Network on the use of myeloid growth factors with cancer chemotherapy: a review of the evidence. *J Natl Compr Canc Netw*. 2005;3:557–571.