a. Paradox with chemotherapy for cancer

The phenomenon where therapy for a first type of cancer has the downstream consequence of causing a second type of cancer has been thoroughly documented (129,130, 131,132,133,134,135,136,137).

Radiation and chemotherapy can inflict damage on the chromosome. Damage to DNA includes strand breaks, apurinic sites, apyrimidinic sites, intrastrand cross-links, interstrand cross-links, and the incorporation of incorrect bases. Cisplatin, for example, cross-links DNA. Methotrexate and 5-fluorouracil result in the incorporation of an incorrect base, namely, uracil. The mechanism of action of radiation and of chemotherapy in cancer therapy is to cause mutations, that is, mutations that are so extensive and severe that the tumor cell cannot survive.

On the other hand, radiation or chemotherapy can also inflict damage on the DNA of normal cells, and in the case where damage is slight and the normal cell survives, and where the damage resulted in a mutation in gene used for cell signaling, cell cycle control, or cell growth, the normal cell may be converted to a cancer cell.

This scenario has been documented in the case of breast cancer. Leukemia following chemotherapy for breast cancer was studied among patients diagnosed during 1973–1985. Among 13,734 women given initial chemotherapy, 24 women developed acute non-lymphocytic leukemia (ANLL), compared to only two women as expected, based on general population rates (138).

[129] Carneiro BA, Kaminer L, Eldibany M, Sreekantaiah C, Kaul K, Locker GY. Oxaliplatin-related acute myelogenous leukemia. *Oncologist*. 2006;11:261–262.

[130] Barzi A, Sekeres MA. Myelodysplastic syndromes: a practical approach to diagnosis and treatment. *Cleve Clin J Med*. 2010;77:37–44.

[131] Flaig TW, Tangen CM, Hussain MH, et al. Randomization reveals unexpected acute leukemias in Southwest Oncology Group prostate cancer trial. *J Clin Oncol*. 2008;26:1532–1536.

[132] Le Deley MC, Suzan F, Cutuli B, et al. Anthracyclines, mitoxantrone, radiotherapy, and granulocyte colony-stimulating factor: risk factors for leukemia and myelodysplastic syndrome after breast cancer. *J Clin Oncol*. 2007;25:292–300.

[133] Beaumont M, Sanz M, Carli PM, et al. Therapy-related acute promyelocytic leukemia. *J Clin Oncol*. 2003;21:2123–2137.

[134] Praga C, Bergh J, Bliss J, et al. Risk of acute myeloid leukemia and myelodysplastic syndrome in trials of adjuvant epirubicin for early breast cancer: correlation with doses of epirubicin and cyclophosphamide. *J Clin Oncol*. 2005;23:4179–4191.

[135] Crump M, Tu D, Shepherd L, et al. Risk of acute leukemia following epirubicin-based adjuvant chemotherapy: a report from the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2003;21:3066–3071.

[136] Chaplain G, Milan C, Sgro C, Carli PM, Bonithon-Kopp C. Increased risk of acute leukemia after adjuvant chemotherapy for breast cancer: a population-based study. *J Clin Oncol*. 2000;18:2836–2842.

[137] Patt DA, Duan Z, Fang S, Hortobagyi GN, Giordano SH. Acute myeloid leukemia after adjuvant breast cancer therapy in older women: understanding risk. *J Clin Oncol*. 2007;25:3871–3876.

[138] Curtis RE, Boice JD, Moloney WC, Ries LG, Flannery JT. Leukemia following chemotherapy for breast cancer. *Cancer Res*. 1990;50:2741–2746.