

prophylaxis starting in the first cycle of chemotherapy can reduce the rates of febrile neutropenia and neutropenia-related hospitalization.

However, the undesired effect of the growth factor may be the following. The anti-apoptotic effect of G-CSF or GM-CSF saves cancer cells, which have been exposed to DNA-damaging chemotherapeutic agents, from destruction, thereby permitting the cancer cells to develop into a myeloid cancer.

Administration of these growth factors has been associated with increased risks for certain neoplastic disorders, including cancer and dysplasia. Dysplasia refers to abnormalities of chromosomal structure that can be precursors to cancer. The use of G-CSF was associated with a doubling in the risk of subsequent acute myeloid leukemia or myelodysplastic syndrome among the population that we studied, although the absolute risk remained low. Growth factors have also been administered to enhance immune response against an anti-cancer vaccine (144). In any situation where the data suggest that a growth factor can be used as a drug against cancer, researchers and the FDA have been unusually cautious.

### c. Paradox with anti-depressants and depression

Anti-depressants can have the effect of increasing depression and inducing suicide (145). This adverse drug reaction can occur when initiating therapy with the anti-depressant. For example, fluoxetine, known by the trade name Prozac<sup>®</sup>, can result in increased depression and increased suicide risk in children and adolescents (146,147). This effect, which has been extensively documented, is distinguished by the following timeline:

- May 2003: Manufacturer notifies FDA of clinical trial data indicating an increased risk of suicidal thoughts and actions in children and adolescents
- October 2003: FDA issues a public health advisory on possible safety risks related to use of anti-depressants
- September 2004: FDA advisory committees vote in favor of recommending that the FDA issue a black box warning on the anti-depressant product labels
- January 2005: Manufacturers are required to begin including a black box warning on anti-depressant product labels.

<sup>144</sup> Parmiani G, Castelli C, Pilla L, Santinami M, Colombo MP, Rivoltini L. Opposite immune functions of GM-CSF administered as vaccine adjuvant in cancer patients. *Ann Oncol.* 2007;18:226–232.

<sup>145</sup> Friedman RA, Leon AC. Expanding the black box—depression, antidepressants, and the risk of suicide. *N Engl J Med.* 2007;356:2343–2346.

<sup>146</sup> Busch SH, Barry CL. Pediatric antidepressant use after the black-box warning. *Health Aff (Millwood).* 2009; 28:724–733.

<sup>147</sup> Leon AC. The revised warning for antidepressants and suicidality: unveiling the black box of statistical analyses. *Am J Psychiatry.* 2007;164:1786–179.