# Risk of leukemia after cancer chemotherapy persists

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While advancements in cancer treatment over the last several decades have improved patient survival rates for certain cancers, some patients remain at risk of developing treatment-related leukemia, according to results of a study published online in *Blood*, the Journal of the American Society of Hematology (ASH).

Chemotherapy is often a highly effective treatment for cancer, but certain drugs have also been shown in a range of studies to increase a patient's risk of developing therapy-related acute myeloid leukemia (tAML), a rare but frequently fatal condition. Thanks to significant advancements in therapy resulting in improved patient survival rates for certain cancers over the last several decades, researchers and clinicians now aim to design treatment regimens that maximize patient survival while minimizing short- and long-term complications.

"In the course of improving interventions and survival rates in many types of cancer, we have learned that certain chemotherapies can cause damage to cells in the bone marrow, increasing a patient's risk of leukemia. However, no recent large-scale studies have evaluated how the risk of treatment-related leukemia has evolved with the changing treatment strategies," said Lindsay Morton, PhD, of the National Cancer Institute (NCI) and lead author of the study.

To examine how the risk of tAML has evolved over time among cancer patients treated with chemotherapy, Dr. Morton and a team of researchers at the NCI's Division of Cancer Epidemiology and Genetics

evaluated data from cancer registries in the U.S. Surveillance, Epidemiology, and End Results (SEER) Program, identifying adult patients ages 20-84 who were diagnosed with cancer (any type) between 1975 and 2008 and who were treated with chemotherapy. SEER data files were reviewed to determine tAML risk based on first type of cancer, time since diagnosis, age at diagnosis, and year of diagnosis.

Among the 426,068 patients whose data were eligible for analysis, Dr. Morton's team confirmed 801cases of tAML, nearly five times more than the number of cases expected in the general population. To help explain the changes in relative risk over time, investigators compared the trends in the data with evolving treatment recommendations and major therapeutic discoveries as described in the medical literature. While patient information in the SEER database did not include data on specific drugs or doses, the incidence trends were consistent with changing treatment practices and the toxicities associated with certain chemotherapies. Notably, the proportion of patients receiving chemotherapy, both with or without radiotherapy, increased during the study period for many malignancies.

As the team compared tAML risks with trends in cancer treatment over time, they analyzed several factors that likely contributed to the differences in risk between patients, including the type of cancer initially diagnosed and the year of diagnosis. For example, trends in risk for breast cancer patients (which comprised roughly one-third of tAML cases in the study) correlated to changes in breast cancer treatment protocols over the last several decades, suggesting that the decrease in tAML risk observed among breast cancer survivors in the 1980s might be attributable to an increased use of cyclophosphamide-based chemotherapy, which is less likely to cause leukemia than earlier treatment options.

A similar decline in risk was observed among ovarian cancer patients,

possibly linked to a shift in ovarian cancer chemotherapy treatment in the 1970s from melphalan, a type of chemotherapy that has been shown to trigger leukemia, to a less toxic platinum-based chemotherapy. In contrast, tAML risks increased over the last several decades among patients treated with chemotherapy for non-Hodgkin lymphoma (NHL), possibly as a result of improvements in survival for patients who received multiple courses of treatment.

Further, Dr. Morton's team identified newly elevated tAML risks for patients treated with chemotherapy since 2000 for esophageal, anal, cervical, and prostate cancers, and since the 1990s for bone/joint and endometrial cancers – risks that could potentially be related to expanding use of chemotherapy in recent years. Patients diagnosed with myeloma today still face some of the highest risks for tAML, possibly due to the ongoing use of melphalan to fight the aggressive disease.

The database analysis also found that relative tAML risk for many patients tended to decline with increasing time since initial cancer diagnosis. For those with non-hematologic malignancies, there was no evidence of elevated tAML risks more than 10 years following diagnosis, whereas risks persisted more than 10 years after diagnosis for patients with Hodgkin lymphoma (HL), NHL, and myeloma. Heightened tAML risk among these patients could be linked to the higher intensity and longer duration of their treatment.

"Future studies should identify patients at the highest risk of tAML so that the risks can be weighed against the benefits of chemotherapy, particularly for cancers with favorable long-term survival," said Dr. Morton. "Further research is also warranted to assess the risks associated with new targeted and immunomodulatory agents by including secondary malignancies such as tAML as endpoints in prospective clinical studies of new agents or new uses of standard agents."