ADVANCES IN LLM

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How Disease Stage Impacts the Rate of Second Primary Malignancies in Patients With Diffuse Large B-Cell Lymphoma

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H&O How common are second primary malignancies among patients with diffuse large B-cell lymphoma (DLBCL)?

MK Nearly 60% of patients with DLBCL can be cured with chemotherapy. These patients are at a slightly higher risk for developing second primary malignancies compared with age-matched controls. The etiology of this occurrence is unknown, but some investigators have hypothesized a relationship to treatments such as chemotherapy, radiation, and rituximab, and perhaps chronic infections or lifestyle practices. The incidence of second primary malignancies among patients with DLBCL is approximately 10% to 15%. Currently, there is no defined tool to predict which patients will develop a second primary malignancy, the types of malignancies likely to develop, or the temporal association.

H&O What types of secondary cancers are most common?

MK In my clinical practice, the most common secondary cancers in patients with DLBCL are those of the prostate, breast, and colon, as well as hematologic malignancies, such as acute myelogenous leukemia and myelodysplasia.

H&O How does the development of second primary malignancies impact prognosis?

MK According to data from clinical trials and retrospective reviews of patients with DLBCL cured at the 5-year mark, overall survival is decreased among those who develop a second primary malignancy. An important area of investigation is screening for second primary malignancies. Earlier detection would allow quicker initiation of therapy that could possibly be curative, thus positively impacting long-term outcomes.

H&O Could you define early-stage vs late-stage DLBCL?

MK Early-stage disease refers primarily to stage 1 and stage 2. Late-stage disease, also called advanced-stage disease, is stage 3 and stage 4. Patients with early-stage disease tend to have a better prognosis than those with advanced-stage disease. They usually receive fewer cycles of chemotherapy, with or without radiation therapy. Patients with bulky tumors receive treatment that is similar to that for advanced-stage disease, even if they are stage 1 or 2.

Research is providing insight into the biology of these 2 stages. Historically, 5 years has been used as the benchmark to indicate a cure. However, an intergroup study led by the Southwest Oncology Group (SWOG) and first-authored by Deborah Stevens, MD, showed that early-stage lymphomas have a tendency toward late relapses, even beyond the 5-year point. In addition, gene-expression profiling studies have shown differences in patients who have early-stage vs advanced-stage disease. The biology, milieu, and treatment options are slightly different between the 2 subtypes, providing the rationale

for the hypothesis of our recent study on second primary malignancies in DLBCL.

H&O What was the design of your study?

MK We aimed to ascertain whether differences in the biologic milieu between early-stage and advanced-stage DLBCL might relate to differences in the types, incidence, and timing of second primary malignancies. This hypothesis has never been explored before. We searched the Surveillance, Epidemiology, and End Results (SEER) research database for adult patients diagnosed with DLBCL between 1973 to 2010, and who were categorized as early stage (stage 1 or 2) or advanced stage (stage 3 or 4). Investigation of the temporal association was based on 5-year intervals. We examined whether the incidence, timing, and type of second primary malignancies were higher in the first 5 years vs the next 5 years, up to 15 years.

The study identified 26,038 patients with DLBCL: 14,724 with early-stage disease and 11,314 with advanced-stage disease. The median follow-up was approximately 13 years. We found that 13% of patients developed second primary malignancies, which was in line with previous studies. Our study showed that patients with early-stage disease tended to have a higher incidence of second primary malignancies. The rate was 14.0% for early-stage disease vs 11.6% for advanced-stage disease. This difference was not statistically significant (P=.14). A surprising finding was that patients with early-stage DLBCL had a higher risk for developing second primary cancers in the 5 years following treatment. These second primary cancers tended to be mostly solid tumors, such as those of the breast, colon, or prostate. In contrast, patients with advanced-stage DLBCL had an increased risk for developing second primary cancers in the 10 to 15 years after successful treatment. Instead of solid tumors, these cancers tended to be hematologic malignancies, including acute myelogenous leukemia and myelodysplastic syndrome.

The study also found that overall survival was decreased among patients who developed a second primary malignancy. The biggest impact on survival was seen among patients who were diagnosed with early-stage disease in the post-rituximab era and who developed a second primary malignancy. It is not known why this cohort had decreased survival as compared with the others, and this observation merits further investigation.

H&O What are the study limitations?

MK This is a registry study with certain confounders. For example, radiation therapy was not associated with second primary cancers. However, in the SEER database, use of radiation is coded as either known or unknown. It may be that some patients categorized as "unknown" did in fact receive radiation. The database does not list the types of chemotherapy that patients received. Disease relapse is also not collected by the SEER database. A decrease in survival could be attributable to relapsed disease.

Within the constraints of this registry study, however, our hypothesis was confirmed that patients with early-stage DLBCL have a unique genetic milieu that may predispose them to second primary malignancies that differ from those reported in patients with advanced-stage disease.

H&O Does the study have implications for clinical care?

MK Decisions in clinical practice should usually be based on data from prospective clinical trials. A larger, multi-institutional prospective trial is needed to validate the observations made in our analysis of the SEER database.

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The study did provide a few insights, however. The study highlights the importance of survivorship among patients with DLBCL. Many patients are surviving this disease, and we lack adequate tools to recognize the secondary malignancies that can occur. The study can help refine clinical care. For example, if a patient with early-stage DLBCL has blood in the stool within 5 years of diagnosis, I would consider recommending a colonoscopy based on the higher risk for secondary primary malignancies—even if he or she is not older. Similarly, if a patient with advanced-stage disease presents with low blood counts 10 years after diagnosis of DLBCL, I would order appropriate blood tests to exclude acute myelogenous leukemia and myelodysplastic syndrome.

H&O Does the study have implications for other types of lymphoma?

MK Our findings have implications for other aggressive lymphomas that are curable. A similar analysis should be performed among patients with indolent lymphomas, which typically are treatable, but not curable. This type of study would also be beneficial in any lymphoma that is treated with genotoxic therapies, such as chemotherapy and/or radiation therapy.

Disclosure

Dr Kamdar is on the speakers bureau of Seattle Genetics. She is a consultant for Pharmacyclics, Janssen, AstraZeneca, and Celgene.

Suggested Readings

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