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621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Incidence and Prognosis of Primary Malignancies in Ataxia-Telangiectasia Patients: A Report from the Ataxia-Telangiectasia Clinical Center (ATCC)

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Biallelic germline mutations in the *ATM* gene result in Ataxia-Telangiectasia (AT), a classic DNA repair disorder associated with a high incidence of primary malignancies. The lack of standardized cancer treatment approaches for patients with AT is believed to contribute to poor survival after diagnosis. Robust characterization of the incidence, outcomes, and *ATM* variant enrichment of large cohorts of individuals with AT who develop malignancies are needed to inform therapeutic decision-making.

The AT Clinical Center (ATCC) at Johns Hopkins Hospital is a large, retrospective cohort that prospectively collects outcomes data on individuals diagnosed with AT in the US. Standardized incidence ratios (SIRs) were used to compare cancer incidence to that of age-, sex-, and year-matched US general population using the SEER database. Standardized mortality ratios (SMRs) and mortality rate ratios were used to estimate mortality risk compared to the general population.

Among 508 total participants with AT, 84 developed cancers (16.5%): 39 non-Hodgkin lymphoma (NHL), 7 Hodgkin lymphoma, 16 leukemia (n=13 of T cell origin), and 22 carcinomas. SIRs were 355.9, 67.4, 45.6, and 18.0, respectively. Median (interquartile range) age at cancer diagnosis was 14.3 years (10.3-22.8), with NHL occurring in the youngest (12.4 years, IQR 7.3-16.7) and solid tumors in the oldest (26.3 years, IQR 18.7-29.0) individuals. The SMR was 24.6 (95% CI: 21.1-28.4) for the overall cohort of AT patients and 232.9 (95% CI: 178.1-299.2) among those with cancer. Median survival following a cancer diagnosis was 2.5 years (95% CI: 0.1-14.4). The post-cancer mortality rate ratio was 2.2 (95% CI: 1.1-4.3, p=0.025) comparing AT patients with cancer treated without dose reduction or for whom dosing was unknown (n=24) versus AT patients with cancer who received dose reduced chemotherapy (n= 38). Among those who received chemotherapy (n=62), 11/24 (45.8%, 95% CI: 25.6-67.2) treated with standard dosing and 24/38 (63%, 95% CI: 46.0-78.2) treated with reduced dosing experienced toxicity (p=0.20). *ATM* variant associations were detected by single variant analysis among 247 patients with AT who had confirmed biallelic *ATM* mutations via whole exome sequencing.

Individuals with AT are at very high-risk of primary malignancies, of which NHL is most common. Prognosis is poor regardless of standard versus dose reduced chemotherapy regimens, which calls for novel therapies.

Disclosures No relevant conflicts of interest to declare.

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