Does Hepatocellular Carcinoma Develop After Treatment of Wegener’s Granulomatosis with Cyclophosphamide?

Key words: Wegener’s granulomatosis, cyclophosphamide, hepatocellular carcinoma

Wegener’s granulomatosis is a distinct clinicopathologic entity characterized by granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis. In addition, variable degrees of disseminated vasculitis involving both small arteries and veins may occur. A well-established treatment for this disease has been cyclophosphamide given orally with corticosteroids (1). However, cyclophosphamide, which is an alkylating agent similar to melphalan, chlorambucil and dihydroxybusulfan, is known to induce tumors in the classical manner associated with chemical carcinogenesis. This agent, in particular, has been related to an increased frequency of hemorrhagic cystitis (2, 3) and bladder cancer (4-7). The effect appears specific for this particular alkylating agent, which induces acute toxic effects in the bladder mucosa.

Cyclophosphamide, a widely used alkylating agent, is helpful in treating patients who have either malignant or nonneoplastic disease. After oral or intravenous administration, the drug is metabolized by hepatic microsomal enzymes to hydroxycyclophosphamide and later by target cells to phosphamide (active) and acrolein (urinary metabolite) (8-10). The mustard component forms covalent linkages with nucleic acids of DNA (alkylation) to inhibit cell replication and produce a cytotoxic effect. Acrolein, however, is responsible for urothelial damage. Animal experiments have shown that cyclophosphamide-induced cystitis is the result of contact between toxic urine and the bladder epithelium (2, 11). Although the entire urinary collecting system is at risk for acrolein-mediated toxicity, the bladder is most susceptible because of its prolonged exposure to the drug. Hemorrhagic cystitis and the induction of bladder cancer are well-recognized complications of oral cyclophosphamide therapy in patients with Wegener’s granulomatosis, systemic lupus erythematosus, and rheumatoid arthritis. However, the incidence of cyclophosphamide-induced cystitis and its relation to the development of bladder cancer have not been defined (6).

Talar-Williams et al reported that nonglomerular hematuria developed in 50% of the patients with Wegener’s granulomatosis who received oral cyclophosphamide (6). Thus, nonglomerular hematuria generally indicates the presence of cyclophosphamide-induced bladder injury. Bladder cancer developed in approximately 5% of the patients treated with cyclophosphamide. This represents a 31-fold increase in the incidence of bladder cancer and a 51-fold increase for persons younger than 65 years of age as compared with the general population. In addition, bladder cancer developed in 12% of the patients with Wegener’s granulomatosis whose cumulative cyclophosphamide dose exceeded 100g (6).

Knight et al identified a population-based cohort of 1,065 patients with Wegener’s granulomatosis in the Swedish Inpatient Register over a period of 26 years (12). Standardized incidence ratios (SIR) between observed and expected numbers of cancers were used as a measure of relative risk. There was a 2-fold overall increased risk in the cohort. The increase was most pronounced for bladder cancer (SIR=4.8), squamous cell skin cancer (SIR=7.3), leukemia (SIR=5.7) and malignant lymphoma (SIR=4.2). The results confirm previous indications of an increased risk for cancer of the urinary bladder but also point to increased risks for cancer at other sites (12). In addition, there are reports showing renal cell carcinoma (13) and papillary adenocarcinoma of the thyroid (14) associated with cyclophosphamide therapy for Wegener’s granulomatosis. However, the occurrence of liver cancer containing hepatocellular carcinoma (HCC) is rare in patients with Wegener’s granulomatosis treated with cyclophosphamide. Okano et al described a case of HCC associated with long-term cyclophosphamide therapy for Wegener’s granulomatosis (15).

The patient took cyclophosphamide for 21 years, and serum markers for HBV and HCV, which are major causes of this tumor, were negative. There was one additional case suggesting an association between cyclophosphamide therapy and the occurrence of HCC. However, in that case, serum HBsAg was positive (16).

The mechanism by which cyclophosphamide treatment may trigger HCC is obscure. Alkylating agents including cyclophosphamide may exert their action in part by breaking chromosomes. This mechanism mimics an effect of ionizing radiation, which is carcinogenic to a variety of organs. Indeed, leukemia, the radiogenic tumor with the shortest latent period, has now been convincingly linked to the use of alkylating agents. In studies of ovarian cancer and myeloma
it was estimated that the incidence of leukemia among patients surviving ten years from treatment with alkylating agents might be on the order of 12–20%. This risk of leukemia may be acceptable when treating conditions with a poor prognosis such as advanced ovarian cancer or myeloma. Acute leukemia has been conclusively linked to the use of alkylating agents, but, probably through immunosuppressive effects (8).

Immunosuppressive agents have been assessed primarily by follow-up studies of renal transplant recipients. In a survey of 16,290 transplant patients the risk of non-Hodgkin’s lymphoma was increased 32 fold. For all other cancers combined, the excess risk was on the order of two fold and first became evident about two years after transplantation. There were modest increases in the risk for cancers of the liver, bile duct and gallbladder and urinary bladder, and for soft tissue sarcoma, leukemia, adenocarcinoma of the lung, squamous carcinoma of the skin and malignant melanoma. The array of neoplasms following drug-induced immunosuppression resembles that seen with the genetically determined immune deficiency syndromes (8). The occurrence of HCC may be related to the long-term immunosuppressive effects associated with cyclophosphamide as an alkylating agent. Although the mechanisms of the occurrence of HCC associated with long-term cyclophosphamide therapy for Wegener’s granulomatosis remain to be elucidated, further study is warranted to clarify the cellular and molecular events underlying this phenomenon.

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References