Reprinted from the Journal of the American Medical Association
February 27, 1981, Volume 245

Effect of Warfarin on Survival in Small Cell Carcinoma of the Lung

Veterans Administration Study No. 75

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• **In a controlled, randomized study, survival of patients with small cell carcinoma of the lung (SCCL) was prolonged on addition of warfarin sodium to combination chemotherapy plus radiation therapy. Median survival for 25 control patients was 24 weeks and for 25 warfarin-treated patients was 50 weeks. This difference could not be accounted for by differences between groups in performance status, extent of disease, age, or sex. The survival advantage associated with warfarin administration was observed both for patients with extensive disease and for those who failed to achieve complete or partial remission. The warfarin-treated group also demonstrated a significantly increased time to first evidence of disease progression. These results suggest that warfarin may be useful in the treatment of SCCL and also support the hypothesis that the blood coagulation mechanism may be involved in the growth and spread of cancer in man.**

(*JAMA* 1981;245:831-835)

IN APRIL 1976, a Veterans Administration Cooperative Study was launched to test the hypothesis that warfarin sodium anticoagulation would favorably modify the course of several forms of malignant disease in man. Details of protocol design, a description of tumor categories under investigation, and a review of previous work in experimental tumor systems and in man that provided the rationale for this controlled, randomized, multi-institutional trial have been presented elsewhere.[1] Briefly, it has been shown in certain experimental tumor systems that inhibition of coagulation reactions by various means results in limitation of tumor growth and spread, while augmentation of coagulation reactions enhances tumor growth and spread. Data pertaining to patients admitted to this study with small cell carcinoma of the lung (SCCL) form the basis of this report.

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METHODS

Fifty patients with histologically or cytologically confirmed SCCL who did not manifest predetermined exclusion criteria[1] and who gave informed consent (in accord with the Helsinki Declaration) were subjected to computer randomization by hospital and performance status to receive combination chemotherapy and radiation therapy with or without warfarin. All patients with SCCL who were seen at participating hospitals were screened for possible entry to this protocol.

Combination chemotherapy and radiation therapy considered to be appropriate at the inception of the study that was given to all patients admitted to this study was adapted from that of Eagan and associates.[2] This consisted of the following: (1) cyclophosphamide, 2,000 mg/sq m intravenously (IV) on day 1 of each 28-day cycle; (2) vincristine sulfate, 1.5 mg/sq m IV on day 1 of each 28-day cycle; (3) methotrexate, 30 mg/sq m IV on day 22 of each 28-day cycle; (4) radiation therapy consisted of 3,200 rad to the primary tumor and the primary drainage area in the mediastinum to 2 cm into the contralateral side and to the infracarinal node area delivered in ten treatments after the second chemotherapy cycle. Warfarin (provided by Elizabeth H. Newkom, MD, of Endo Laboratories) was administered to patients in doses intended to prolong the prothrombin time to approximately two times the control value. Warfarin treatment was started within 24 hours of randomization.

The criteria used to define response to treatment have been described elsewhere.[1] Serial examinations and tumor measurements were obtained at intervals of no greater than four weeks corresponding to the chemotherapy cycles. The distinction between limited and extensive disease[3] was made on the basis of routine x-ray and laboratory tests, together with bone marrow aspiration studies and radioisotope scans of the brain, liver, and bones.

Survival curves were computed according to the method of Kaplan and Meier.[4] The modification of the Wilcoxon tests by Gehan[5] was used to test for statistical significance between the survival curves for the warfarin-treated and control groups. The χ^2 test was used to compare qualitative characteristics between the warfarin and control groups, while the two-sample t test was used to compare quantitative characteristics between the two groups. All statistical tests used were two-sided.