RATIONALE AND EXPERIMENTAL DESIGN FOR THE VA COOPERATIVE STUDY OF ANTICOAGULATION (WARFARIN) IN THE TREATMENT OF CANCER

LEO R. ZACHARSKI, MD,*† WILLIAM G. HENDERSON, PHD,‡
FREDERICK R. RICKLES, MD,§ WALTER B. FORMAN, MD,‖ C. J. CORNELL, JR., MD,†
R. JACKSON FORCIER, MD,† HAROLD W. HARROWER, MD,†
AND ROBERT O. JOHNSON, MD¶

Anticoagulants have been demonstrated to reduce tumor growth in certain experimental animal systems. Inhibition of clot formation interferes with tumor growth and spread while enhancement of coagulation promotes tumor growth and spread. The fact that the coagulation mechanism is commonly activated in human malignancy together with preliminary reports of therapeutic efficacy of anticoagulants suggests that the coagulation mechanism may be of pathophysiologic significance also in the growth of human tumors. A VA Cooperative Study has been established to test the hypothesis that warfarin anticoagulation will modify the course of malignancy in man. The purpose of this paper is to present the rationale and experimental design for this study with emphasis on management of anticoagulant administration in cancer patients. This paper serves as the basis for forthcoming reports of toxicity and therapeutic efficacy of warfarin in human malignancy.

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EVIDENCE SUPPORTING the efficacy of anticoagulants in the treatment of certain malignant tumors in experimental animals has recently been reviewed.[25,30,38,41,50,73,91] Agents which successfully inhibit tumor spread in

From the *VA Hospital, White River Jct., Vermont and the †Norris Cotton Cancer Center, Dept. of Medicine, Dartmouth-Hitchcock Medical Center, Hanover, New Hampshire; ‡Cooperative Studies Program Coordinating Center, VA Hospital, Hines, Illinois; and Dept. of Clinical Pharmacology and Therapeutics, Loyola University School of Medicine, Maywood, Illinois; §VA Hospital, Newington, Connecticut and Dept. of Medicine, University of Connecticut, School of Medicine, Farmington, Connecticut; ‖VA Hospital, Cleveland, Ohio and Dept. of Medicine & Pharmacology, Case Western Reserve University, School of Medicine; #VA Hospital, Providence, Rhode Island and the Dept. of Surgery, Brown University Medical School; ¶Dept. of Surgery & Human Oncology, University of Wisconsin Medical School, Madison, Wisconsin.

The authors constitute the Study Executive Committee. *Study Chairman. ‡Study Biostatistician.

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Participants: Stephen Davis, MD; William C. Lowe, MD; VA Hospital, East Orange, New Jersey. Philip De Simone, MD; VA Hospital, Lexington, Kentucky. Walter B. Forman, MD; VA Hospital, Cleveland, Ohio. Joseph F. O'Donnell, MD; Dennis Hammond, MD; Carolyn Mook, MD; VA Hospital, White River Jct., Vermont. Harold W. Harrower, MD; VA Hospital, Providence, Rhode Island. Elwood Headley, MD; VA Hospital, Gainesville, Florida. Sang-Hee Kim, MD; VA Hospital, Cincinnati, Ohio. Hau Kwaan, MD; VA Hospital (Lakeside), Chicago, Illinois. Robert O'Dell, MD; Karl Eurenius, MD; VA Hospital, Charleston, South Carolina. Frederick R. Rickles, MD; Richard Edwards, MD; VA Hospital, Newington, Connecticut. Lloyd Rogers, MD; VA Hospital, Syracuse, New York. Karl Tornyos, MD; VA Hospital, New Orleans, Louisiana. Herbert Wohl, MD; VA Hospital, San Diego, California.

VA Central Office: James Hagans, MD, PhD, Chief, Cooperative Studies Program, VACO, Washington, D.C.

Address for reprints: Leo R. Zacharski, MD, VA Hospital, White River Jct., VT 05001.

Cooperative Studies Program Coordinating Center, VA Hospital, Hines, Illinois: Kenneth E. James, PhD, Chief; William G. Henderson, PhD, Biostatistician; Shig Ochi, PhD, Past Assistant Chief; Joseph Lapidoth, MS, Statistician-Programmer.

Operations Committee: Emil Frei, III, MD, Sidney Farber Cancer Institute, Boston, Massachusetts; George B. Hutchison, MD, Harvard University School of Public Health, Boston, Massachusetts; Marvin Zelen, PhD (Chairman), Sidney Farber Cancer Institute, Boston, Massachusetts.

Cooperative Studies Program Central Research Pharmacy; Mike R. Sather, R Ph, MS, Chief, VA Hospital, Albuquerque, New Mexico; John P. Van Eckhout, RPh, VA Hospital, Albuquerque, New Mexico.

Past Research Pharmacists: Marina Y. Chang, RPh, VA Hospital, Washington, D.C.; Larry M. Young, RPh, VA Hospital, Albuquerque, New Mexico.

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experimental systems include heparin; warfarin; platelet-inhibitory agents, such as aspirin,[24] dextran,[74] and dipyridamole and its derivatives[5,25]; polyamines,[41] which inhibit fibrin-stabilizing factor (factor XIII); fibrinolytic agents which convert plasminogen to plasmin, such as urokinase and streptokinase; and Arvin or Ancrod, which induce hypofibrinogenemia.[88,92] In contrast, conditions which enhance coagulation increase experimental metastasis formation.[2,25,38,41,50,91] Examples of such conditions include administration of antifibrinolytic agents, such as epsilon amino caproic acid (EACA); induction of hyperfibrinogenemia; injection of ellagic acid, which activates factor XII;[2] injection of cultured fibroblasts, which contain the procoagulant known as tissue factor (TF or thromboplastin), along with tumor cells;[24] and administration of endotoxin which stimulates tissue factor activation in leukocytes.[42,50,60] Peters and Hewitt[55] have presented evidence suggesting that the so-called Revesz effect (that is, the increase in the number of tumor takes when nonviable tumor cells are injected with the viable cells) is mediated by the thromboplastin present in the nonviable cells. Inhibition of the growth and spread of experimental tumors by anticoagulation may be due to the direct effects of coagulation inhibition, or anticoagulation may potentiate either an immunotherapeutic or chemotherapeutic attack on the tumor.[3,9,11,24,30,32,33,36,39,40,48,62,74,76–80,84,88,92]

The uptake of radioisotopically labelled fibrinogen by tumor tissue occurs in many types of malignancy[5,7,15–17,43,45,56,67,70,71] and is reduced by anticoagulants in association with a more favorable course of the tumor.[67] It has been postulated that clot formation at the tumor periphery may: 1) facilitate attachment of metastatic tumor cells to endothelial cells (tumor cells which fail to adhere do not survive); 2) provide nutrients and/or growth stimulants; 3) serve as a structural lattice upon which tumor cells can proliferate; or 4) protect the tumor cells from host defense mechanisms.[30,91] Perhaps more than one of these alternatives obtain.

EXPERIMENTAL STUDIES

Studies in experimental animals have suggested that anticoagulants are beneficial by virtue of their inhibitory effect on the clotting mechanism. This conclusion has been strengthened, at least for the drug warfarin, by the demonstration that the antimetastatic effects of warfarin are reversed by simultaneous administration of sufficient vitamin K to inhibit its anticoagulant effect.[11] Other studies, however, have suggested that anticoagulants might have direct anti-tumor effects. For example, it has been shown that warfarin is cytotoxic and inhibits tumor cell motility *in vivo*.[25,38,41,50,91] Kirsch *et al.*[40] have demonstrated a synchronization effect of warfarin on glioblastoma cells in culture. Van Buskirk and Kirsch[82] also demonstrated that warfarin administration resulted in reduced cytoplasmic RNA in mouse hepatoma cells implanted subcutaneously but had no effect on normal liver. Chang and Hill[12] found that warfarin reduced DNA and RNA synthesis in L1210 leukemic cells. All of these studies suggest that warfarin may possess other properties which might modify tumor cell metabolism *in vivo* and make these cells more susceptible to chemotherapeutic agents. In addition, heparin and plasmin can be cytotoxic[25,38,41,50,91] while heparin and streptokinase have been shown to enhance the cell-killing effect of nitrogen mustard.[3]

Platelet turnover is increased in patients with malignancy.[29] Administration of aspirin and dipyridamole in doses sufficient to inhibit the *in vitro* platelet-collagen interaction and to prolong the bleeding time *in vivo*, and in doses which have been shown to reduce abnormal platelet consumption in other conditions,[26] failed to improve abnormal platelet consumption when administered to patients with cancer.[1] Nevertheless, both drugs have antimetastatic properties in experimental tumors.[24,25] This suggests that the carcinostatic activity of these platelet inhibitors may be a direct antitumor effect rather than related to their antihemostatic properties.

Agents which interfere with blood coagulation might also manifest antitumor activity by modifying host immunologic defense mechanisms. In this regard, it has been shown that induction of fibrinolysis enhances cellular immune reactions.[76,78] Heparin causes lymphocytosis in certain experimental animals and could modify immunity also.[21,36]

An additional line of evidence which links the blood coagulation mechanism to the pathophysiology of malignancy consists of the increased incidence of both localized thromboembolic disease and disseminated intravascular coagulation (DIC) in malignancy.[4,54] The association of malignancy with throm-

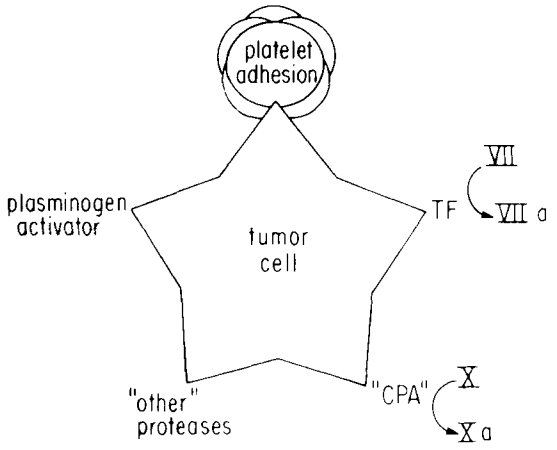

FIG. 1. Proposed mechanisms of interaction between malignant cells and the blood coagulation mechanism include: activation of factor VII by tissue factor (TF),[27,28,64,65] activation of factor X by so-called cancer procoagulant A ("CPA"),[26] activation of coagulation by other proteases[57,58] production of plasminogen activator[14,59] and adhesion of platelets to tumor cell surfaces.[87] It is not likely that activation of coagulation via the Hageman factor (XII) pathway occurs in malignancy.[44]

boembolic phenomena has been recognized for over 100 years and has recently been extensively reviewed.[63] Through careful analysis of a large series of cancer patients, a significantly increased incidence of thromboembolic disease has been documented in comparison to patients with nonneoplastic disease.[4]

One explanation for induction of both localized and disseminated intravascular coagulation in these patients is that a tumor-related procoagulant(s) is introduced to the circulation. Malignant cells have been shown to contain both TF and a procoagulant capable of directly activating factor X (the so-called cancer procoagulant A).[26,27,51,93] The availability of either TF or any enzyme which can activate factor X in the vasculature may be manifested at localized sites distant from the tumor (in the form of thromboembolic disease) or throughout the circulation (in the form of DIC). Notable accumulation of platelets and fibrinogen have been demonstrated at the tumor sites.[15,17,56,67,69,72] Thrombi, demonstrated by a variety of light, fluorescent and electron microscopic techniques,[8,31,37,52,53,66,69,75,85,86] have been observed surrounding embolic tumor masses and malignant cells have been observed to proliferate within these thrombi.[66] As mentioned above, radioisotopically labelled fibrinogen (or antibody to fibrinogen) has been shown to accumulate at tumor sites.[15,17,56,67,69,72]

A summary of the proposed relationships linking the clotting mechanism to the pathogenesis of malignancy is presented in Fig. 1. While these experimental studies in animals are of interest, it is perhaps more relevant to review the current knowledge regarding blood coagulation and human malignancy.

Anticoagulants and Human Malignancy

A relationship between local fibrin formation and human malignancy has been recognized for over a century. In 1878, Billroth[10] described the existence of tumor cells within a thrombus in humans and related this association to metastasis formation. He proposed that metastases formed when fragments of tumor-bearing thrombi embolized from the parent thrombus. This association was reiterated shortly after the turn of the century.[68] In 1915, Iwasaki[35] described thrombi in association with metastatic foci in a variety of human tumor types and demonstrated viable, mitotic cells inside vascular channels within recanalizing thrombi. In 1934, Willis[89] observed thrombus formation over tumor cells invading a blood vessel and concluded that the blood clot constituted a suitable culture medium for tumor since the cells appeared healthy and were proliferating. In 1947, Saphir[66] studied microscopic tumor emboli in a variety of human malignancies and found fresh thrombi surrounding nests of tumor cells. Saphir emphasized again the healthy appearance of the cells. Two years later, Morgan[49] recognized that thrombi were associated with the majority of instances of tumor embolization in man. The latter was subsequently confirmed by Durham *et al.*[20] and by Winterbauer *et al.*[90]

More recently, various histochemical,[52,53] immunologic and radioisotopic[2,43,45,72,73] procedures have permitted detection of fibrin in human tumors. Unfortunately, these promising techniques have never been applied systematically in clinical studies in order to determine pathophysiologic relationships. It is not known whether anticoagulants interfere with fibrin deposition in human malignancy.

Several studies of the effects of anticoagulants on tumor homeostasis in man have been carried out in recent years. Following a pilot study of oral anticoagulants in 96 patients with advanced cancer which was designed to determine toxicity,[81] Thornes[79,82] reported that patients with certain types of

malignancy required a lower maintenance dose of chemotherapeutic agents (reduction to approximately 25% of the initial dose) to control their disease following initiation of warfarin therapy. In subsequent studies, he reported the results of oral anticoagulant therapy in 128 patients with advanced cancer.[79,80] Alternate patients with malignancy of similar histological type were given warfarin in addition to chemotherapy or chemotherapy alone. The two-year survival in the warfarin-treated group was 40.6% in contrast to 17.8% in the control group ($p \leq 0.01$). While this study encompassed a wide variety of tumor types, it was Thornes' opinion that ovarian cancer, breast cancer, and lymphosarcomas (including lymphatic leukemia), were particularly responsive to warfarin.[80] Preliminary data contained in the same report indicated a beneficial effect of fibrinolytic therapy in tumor treatment but results were too early to be definitive.[80]

Recently, Thornes' group reported a study of 44 patients with advanced (stage IV) breast cancer.[82] Half of these patients received conventional chemotherapy and half received chemotherapy together with B.C.G., levamisol and warfarin. Median survival was 17 months in the former group and 34 months in the latter group. Interpretation of these seemingly clear-cut results is confounded by the fact that both immunostimulation and anticoagulation were used in the experimental group having the longer survival.

Several patients with acute leukemia have been treated with a fibrinolytic agent with or without warfarin.[77] Remission was achieved in many of these cases.

Drapkin *et al.*[18] recently reported data suggesting that patients with acute promyelocytic leukemia were more likely to achieve remission when treated prophylactically with heparin during initial chemotherapy. This beneficial effect was attributed to amelioration of disseminated intravascular coagulation by heparin which, in turn, resulted in reduction in hemorrhagic complications.

Elias *et al.*[22,23] showed in a small group of patients that heparin anticoagulation, while having no antitumor effect by itself, potentiated the tumor response to a combination of cytotoxic agents. Regression was reported in tumors regarded as highly resistant to chemotherapy, such as squamous cell carcinoma of the lung. However, Edlis *et al.*[21] reported an objective response in only one of 19 patients with lung cancer who were treated with heparin and cyclophosphamide. Similarly, Rohwedder and Sagastume[61a] concluded that heparin had no beneficial effect in 16 patients with lung cancer that they treated. These studies have the disadvantage of being uncontrolled.

Waddell,[84] in an uncontrolled study, suggested that patients with pancreatic carcinoma who were treated with warfarin combined with 5-fluorouracil lived "slightly longer" than patients who were either untreated or who received other forms of therapy. Reis *et al.*[61] have reported their experience when anticoagulants were administered to patients with stage II and III carcinoma of the uterine cervix in order to prevent thromboembolic complications. Among 1,393 women who received conventional therapy but no anticoagulation, the recurrence rate at 18 months was 22.9%. By contrast, the recurrence rate among patients who were apparently identical otherwise but who received anticoagulants was 12.6%. Survival was also increased but the statistical significance of the difference was not presented. This study was retrospective and therefore uncontrolled. Williams and Maugham[86] reported regression of breast, lung and colon cancers upon initiation of Ancrod therapy which induces hypofibrinogenemia. Hoover *et al.*[34] used warfarin anticoagulation as an adjunct to amputation for osteosarcoma. The warfarin was initiated seven days preoperatively and continued during the surgical procedure and then up to six months postoperatively. Despite the relatively small numbers of patients and the fact that comparison was made with retrospective controls, a significant improvement in survival was found in the anticoagulated group.

Michaels[46,47] determined the incidence of malignancy in a group of patients residing in Manitoba, who were previously treated with anticoagulants. Five hundred forty anticoagulated patients were followed a total of 1569 patient years. Patients were treated with warfarin for 3 to 111 months for a variety of cardiovascular diseases. The incidence of malignancy in this group was compared to the incidence of malignancy in an age- and sex-matched population from the Province of Manitoba at large. While the incidence of potentially lethal visceral malignancy was the same in both groups, the number of deaths in the anticoagulant-treated group was signifi-

TABLE 1. Tumor Therapy Schedule (Other than Warfarin)

Category	Organ	
1 and 2	Lung (nonoat cell)	Cyclophosphamide, 1100 mg/m^2 Intravenously, every 3 weeks
3	Lung, oat cell	Cyclophosphamide, 2000 mg/m^2 Intravenously on day 1 and day 29 (first two cycles) and then 1500 mg/m^2 every 28 days for cycles 3 to 6.
		Vincristine, 1.5 mg/m^2 Intravenously on day 1 and every 28 days for 6 cycles.
		Methotrexate, 30 mg/m^2 Intravenously on day 22 of each of the 28 day cycles.
		3200 rads to the primary tumor and the primary drainage area in the mediastium to 2 cm into the contralateral side and to the infracarinal node area to be given in 10 treatments.
4	Colorectal	5-fluorouracil 12 mg/kg. Intravenously daily for 5 days, then 15 mg/kg weekly. Consider the first day that the loading dose is given to be day 1 and commence the weekly injections beginning with day 15.
5	Prostate	Diethylstilbestrol 3 mg/d by mouth daily.
6	Head and Neck	Methotrexate 50 mg/m^2 p.o. or iv, once per week.
7 and 8	Lung and Colorectal, postresection, no residual disease evident	None.
9	Miscellaneous	Stratum reserved for tumor types not currently under investigation in this study.
10	Lung (nonoat cell) Postradiation therapy, no residual disease evident	5000 or more rads in 5 weeks (tissue dose fraction = 82).

cantly reduced. While eight deaths were expected, only one was observed and this was a man with carcinoma of the lung whose tumor was lethal because of direct extension to mediastinal structures. Only a single metastasis to bone was evident. The difference between the anticoagulant-treated and control groups could not be accounted for by earlier diagnosis because of induction of gastrointestinal bleeding by anticoagulants, or earlier demise of treated patients because of attendant cardiovascular disease. Unfortunately, the number of cases reported in this series was relatively small and the relative frequency of various tumor groups could not be determined.

VA Cooperative Study #75: Anticoagulants in Rx of Ca (Warfarin)

In April 1976, a five-year multi-hospital study was launched to test the hypothesis that warfarin anticoagulation would favorably modify the course of human malignancy. The effects of conventional therapy, defined in Table 1, are being compared to conventional therapy plus warfarin in patients with carcinoma of the head and neck, lung, colon and rectum, and prostate. These tumors were chosen for study because they are commonly encountered in the VA hospital system. Warfarin was the anticoagulant selected for this study because of its proven safety when administered on a long-term basis. The therapeutic dose of warfarin has been clearly established and the risk of toxic overdosage can be minimized by monitoring the prothrombin time. Side effects other than hemorrhage are rare and the effects of warfarin excess on the coagulation mechanism can be readily reversed by parenteral vitamin K and/or transfusion therapy.

All patients at participating hospitals with malignancy of a site under investigation are screened for eligibility for entry into the study. Exclusion criteria, presented in Table 2, are primarily intended to reduce to a minimum the inclusion of patients in whom the risks of anticoagulation might be excessive. Minimum data are collected on excluded patients to determine the reasons for exclusion and whether included patients are representative

of the total population of cancer patients seen at participating hospitals.

Informed consent is obtained from eligible patients after being given a description of the study and its rationale, treatment alternatives, potential risks and benefits of treatment, and special instructions in the event that they receive warfarin. The latter includes the need to: 1) maintain constancy of diet, 2) avoid excessive alcohol, 3) avoid other medications unless approved by the physician in order to prevent possible drug interactions which would modify the anticoagulant effect of warfarin, and 4) to have blood tests necessary to monitor the anticoagulant dose. In addition, the patient is given a simple explanation of how the drug is thought to work and procedural instruction in the event of injury or appearance of bleeding.

Patient therapy is determined by random selection within one day of anticipated initiation of therapy. Randomization is done within tumor strata defined in Table 3, performance status** and hospital. Patients randomized to receive warfarin are issued an identification card which states they are receiving this drug. Warfarin anticoagulation is initiated with a dose of 10 mg per day for the first three days followed by adjustment to a dose sufficient to maintain the one-stage prothrombin time within the established therapeutic range for the particular thromboplastin reagent used to perform the prothrombin time. In appropriate strata (see Table 1) and for patients randomized to receive warfarin, chemotherapy is instituted following one week of anticoagulant therapy. In the event of recent surgery, warfarin is not started sooner than seven days postoperatively. Participation in the study does not preclude the use of other therapeutic modalities provided that the prescribed chemotherapy, and not alternative chemotherapy, is given. For example, radiation therapy may be given when indicated to patients in strata other than stratum 3 in which case warfarin is administered simultaneously. In other patients, a surgical procedure may be necessary, in which case warfarin is discontinued two days preoperatively and resumed seven days postoperatively. Warfarin is withheld at such a time as the platelet count falls below 50,000/mm^3 for any reason. Patients manifesting clear-cut tumor progression (see Table 6) on at least two successive examinations may be placed on alternative chemotherapy at the discretion of the attending physician. Required minimum clinical and laboratory tests obtained at specified time intervals are presented in Table 4.

Many of the logistical aspects of the study, such as screening the hospital census for entry or exclusion of patients from the study, maintenance of flow sheets, and communications with the office of the Study Chairman are facilitated by a physician extender (nurse practitioner or medex) employed through the study at each participating hospital.

A single lot of warfarin (Coumodin®) is being used at all participating hospitals.†† Every effort is made to maintain warfarin treatment as long as possible. Only severe bleeding (see Table 5) or other idiosyncratic or allergic reaction is considered to be a defini-

TABLE 2. Criteria for Exclusion from Study

1. Active GI bleeding or peptic ulcer within prior six months
2. Other internal bleeding
3. Prior intercranial hemorrhage
4. Hereditary hemorrhagic disorder
5. Acute pancreatitis
6. Biliary obstruction
7. Hepatic decompensation (on basis other than malignancy)
8. Active hepatitis (SGOT >5 times normal)
9. Advanced renal disease (Creatinine >4.0 mg/dl)
10. Advanced cardiac disease (NYHA Class III or greater)
11. Severe hypertension (diastolic over 115 mm Hg on 3 or more determinations)
12. Allergy or idiosyncratic reaction to warfarin
13. Platelet count <50,000
14. Prothrombin time above 16 seconds for 7 days or more
15. Patient judged not able to follow instructions
16. Patient judged not willing to keep follow-up appointments
17. Patient on other protocols for cancer treatment
18. Patient on warfarin at randomization
19. Patient under 21 years
20. Patient pregnant
21. No histologic diagnosis is made (does not apply to prostate)
22. Patient with multiple malignancy (except where second malignancy is skin cancer other than melanoma)
23. Patient with skin cancer as primary malignancy
24. Patient unaware of cancer and will not be told
25. Patient refuses (if so, the reason is recorded)
26. Physician refuses (if so, the reason is recorded)
27. Patient's anticipated survival is less than 2 months
28. Patient is bedridden

** Performance status (grade:definition): 0:Normal Activity. 1:Impaired (symptomatic but ambulatory). 2:In bed less than 50% of waking hours. 3:In bed over 50% of waking hours. 4:Bedridden.

†† Coumadin® was provided at no cost to the study by Dr. Elizabeth Newkom of Endo Laboratories, Garden City, New York.

TABLE 3. Definition of Tumor Categories

1) *Lung*: limited disease: all cell types except oat cell; initially inoperable or recurrent following previous operation but disease limited to one hemithorax. To qualify for this category the ipsilateral scalene nodes may be involved and the mediastium may be involved bilaterally but there will be no pulmonary parenchymal or pleural disease on the contralateral side.
2) *Lung*: disseminated disease: all cell types except oat cell; disseminated disease.
3) *Lung*: oat cell (small cell); all cases.
4) *Colorectal*: adenocarcinoma; disseminated or locally recurrent disease. Patients suspected of having localized disease but who, at surgery, are found to have spread of the disease beyond colon and regional nodes will be considered to have disseminated disease regardless of whether resection was or was not carried out.
5) *Prostate*: adenocarcinoma; all patients must have x-ray or bone scan evidence of disseminated disease.
6) *Head and neck*: epidermoid carcinoma; all patients will have recurrent or progressive disease subsequent to adequate primary treatment. (Tumors of the lip and salivary gland are excluded.)
7) *Lung*: all cell types except oat cell; postresection in which a "curative" procedure was used.
8) *Colorectal*: adenocarcinoma; Duke's C (penetration through serosa and/or involvement of regional modes); postresection in which a "curative" resection was used, i.e., resection of the lesion and associated mesentery.
9) Stratum 9 was reserved for a number of types of malignancy which are not currently under investigation in this study.
10) *Lung*: all cell types except oat cell: postirradiation therapy with no evidence of disseminated disease.

tive reason for permanent cessation of anticoagulation.

Our intention is to follow every patient admitted to the study until death or until the end of the study. A three-year patient entry period and two-year followup period is anticipated. One type of data analysis will include all randomized patients while a second will include patients only if they were treated with anticoagulant for at least two weeks or survived at least two weeks in the non-anticoagulated group. The primary response criterion is survival. However, tumor responses (see Table 6 for definitions), bleeding complications (see Table 5 for definitions), results of laboratory tests, causes of death and autopsy findings are also being compared between treatment groups.

TABLE 4. Minimum Laboratory and Clinical Examination Schedule

1. *All patients*. The following are performed at prescribed chemotherapy intervals but no less than every 4 weeks:
   A. History, physical exam, weight, performance status.
   B. Prothrombin time, hemoglobin, hematocrit, leukocyte count and differential, platelet count, SGOT, alkaline phosphatase, bilirubin, blood urea nitrogen, creatinine, uric acid, calcium, urine, and stool for occult blood.
2. *Patients randomized to receive warfarin*. The following are performed at intervals no less than every 2 weeks:
   A. Prothrombin time, hemoglobin, hematocrit, platelet count.

CONCLUSION

Achievement of hemostasis is generally conceded to be the reason for the existence of the blood coagulation mechanism. Elements of this mechanism include physical interactions at the surfaces of certain cells, such as platelets and endothelial cells; induction of enzymatic reaction sequences by cell surface-related enzymes, such as TF and plasminogen activator; and the extended but limited and selective proteolysis which occurs upon conversion of circulating coagulation factor proteins from their inactive proenzyme form to their active enzyme form.[59] The significance of such reactions which result in formation and dissolution of clots is widely appreciated. Perhaps somewhat less widely appreciated is the imposing evidence which assigns an essential role for these reactions in a variety of seemingly unrelated homeostatic regulatory mechanisms. Inflammation, wound healing, embryogenesis and tissue remodelling are phenomena in which

TABLE 5. Classification of Hemorrhagic Complications

Grade	Description
0	None
1	Minor, superficial, locally controllable or self-limited bleeding which may not require change of anticoagulant therapy.
2	More significant bleeding which, in the judgment of the attending physician warrants stopping anticoagulant therapy but which is self-limited and not arising from a definable source (no specific bleeding lesion demonstrable). Anticoagulation may be resumed at a later date, perhaps at a lower dose.
3	Serious bleeding which, because of persistence or demonstration of a bleeding lesion, would preclude reinstitution of warfarin.
4	Acute life-threatening bleeding (for example, intracranial bleeding).

TABLE 6. Definition of Tumor Response

Response	Measured lesions	Counted lesions	Measured and counted lesions
1: Complete Remission	a. Complete disappearance of all lesions and symptoms	f. Complete disappearance of all lesions and symptoms	k. Both a and f
2: Partial Remission	b. Decrease of 50% or more in product(s) of diameters in 2 successive visits compared to pretreatment, with no new lesions	g. Decrease of 50% or more in number of lesions, with no new lesions	l. b and/or g with no progression
3: No Change	c. Increase or decrease in products of diameters of less than 50%, with no new lesions	h. Decrease of less than 50% in number of lesions, with no new lesions	m. Both c and h
4: Progression	d. Increase of more than 50% in product(s) of diameters; new lesions; progression of abnormal clinical or laboratory determinations	i. Any increase in number of lesions	n. d and/or i
5: Progression after Remission	e. Increase in product(s) of diameters representing 25% or more return to pretreatment size	j. Appearance of new lesions	o. e and/or j

reactions familiar to the coagulationist are intimately linked.[59] It also appears that such reactions may profoundly modify the local environment of cells thereby providing a setting in which malignant cells may proliferate and spread. These reactions lend themselves to therapeutic manipulation.

Conventional cancer chemotherapeutic agents are usually cytotoxic drugs which, when successful, have a greater toxic effect on the tumor than on the host. Immunotherapy and anticoagulant therapy are aimed at enhancing host response to the tumor. Preliminary data available from studies in experimental animals and in humans suggest the need for a controlled, randomized clinical trial of anticoagulation in human malignancy.

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