Effectiveness of Warfarin among Patients with Cancer

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BACKGROUND: Among patients treated with warfarin for venous thromboembolism (VTE), cancer patients have more thrombotic and hemorrhagic events than patients without cancer. Is this also the case when cancer patients are anticoagulated for other indications?

OBJECTIVE: The objective of the study is to evaluate the effectiveness of warfarin, given for any indication, among patients with cancer in a community setting.

METHODS: We identified patients with cancer from a larger prospective cohort of 6,761 patients from 101 clinical sites in the United States, matched to controls without cancer. The proportion of time spent in the therapeutic range, international normalized ration (INR) variability, and the rate of thromboembolic and major hemorrhagic events were compared between the two groups.

RESULTS: Ninety-five patients undergoing treatment for cancer were matched to 283 patients without cancer. The cancer group spent less time in the target INR range (54 vs 66%, $P<.001$) and had more variable INR values (standard deviation around the mean INR value 1.30 vs 0.71, $P<.001$). There were more thrombotic events in the cancer group than in the control group (5 vs 0 events, $P<.001$). These analyses were repeated after excluding all of the patients anticoagulated for VTE; the results were unchanged.

CONCLUSIONS: Compared to matched controls, cancer patients receiving warfarin spend less time in the target INR range, have more variable INR values, and have more thrombotic events. These effects are not dependent on whether the patient is anticoagulated for VTE or another indication.

KEY WORDS: warfarin; anticoagulation; oncology; cancer; thrombosis.
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INTRODUCTION

For many years, the mainstay of outpatient anticoagulation has been the oral vitamin K antagonist warfarin, a drug with a

narrow therapeutic window. Patients with cancer may experience especially erratic control of the international normalized ratio (INR).¹ Contributing factors may include drug interactions, fluctuations in dietary vitamin K intake, therapy interruptions, hepatic dysfunction, mucositis, and diarrhea and the hypercoagulable state induced by the cancer itself.^{2–10}

In response to two randomized controlled trials that convincingly showed the superiority of low molecular weight heparin (LMWH) in the treatment of VTE among cancer patients,^{11–13} national expert consensus panels have recommended the use of LMWH for patients with VTE and cancer for at least the first 3 to 6 months of long-term treatment.^{14,15} In the study by Lee and colleagues, patients assigned to LMWH had less recurrent VTE (HR 0.48) and decreased mortality (HR 0.50), with no significant difference between groups in the rate of bleeding.^{11,12} However, while these studies provide high-quality evidence that LMWH is superior to warfarin in cancer patients with VTE, there is little evidence regarding the effectiveness of warfarin in cancer patients when it is used for other indications than the treatment of VTE.

The goal of our study was to compare INR control and clinical outcomes between patients with and without cancer, regardless of the indication for warfarin. The Anticoagulation Consortium to Improve Outcomes Nationally (ACTION) study is a large prospective cohort study designed to assess the management of warfarin in community practice within the United States. From this cohort, we identified a population of patients undergoing active treatment for a malignancy to study the effectiveness of warfarin in this setting.

METHODS

The Anticoagulation Consortium to Improve Outcomes Nationally

Study patients were identified from the 6,761 patients enrolled in a prospective cohort study to assess anticoagulation care in the United States, the ACTION cohort, which has been described elsewhere.¹⁶ Briefly, physician practices that were registered users of CoumaCare® software (Bristol-Myers Squibb, Princeton, NJ) were invited to participate by letter and through a study website. CoumaCare® is a software program that was freely available and used by many anticoagulation management services for clinical purposes such as patient tracking, data entry, and record keeping.

All of the 101 participating sites had at least one dedicated provider managing warfarin, usually within the setting of a

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community-based, physician group practice. Patients were invited to participate by letter or in person (at the time of a routine appointment). To be eligible, patients had to be 18 years of age or older and provide written informed consent. For all centers, McKessonHBOC, the data management firm, provided individual on-site training about how to recruit patients, obtain consent, and transmit data. Adverse event reporting was mandatory and study personnel were trained to carry out such reporting in accordance with federal regulatory requirements. Enrollment began in April 2000 and ended in February 2002.

Data Management

Encrypted data from each site were transmitted to the data-coordinating center weekly. Data included demographic information, indication for warfarin therapy, INR target range, medical diagnoses, INR values, warfarin dose, and patient clinical management progress notes. Missing data fields and data entry errors were flagged and resolved directly with the sites by McKessonHBOC before data were transferred to the study investigators. Any interval of 45 days or more without INR testing or any INR value >10 or <0.8 triggered a direct query from the data coordinating center. Resolution of the flag relating to the INR testing interval required validation of continued warfarin use and confirmation that the gap was not related to an adverse event. Study investigators were blinded to the identification and location of participating practices and patients.

Identification and Eligibility of Case-Patients with Cancer

All 102,728 progress notes of the 6,761 enrolled patients were reviewed for documented evidence of an active malignancy. To be eligible for inclusion, patients had to be actively engaged in treatment with chemotherapeutic or hormonal agents, radiation therapy, or palliative care. Patients whose cancer was effectively treated with surgery alone were excluded, as were patients with an observation period of less than 30 days. We also excluded patients whose target INR range encompassed a value lower than 2.0 or higher than 3.5.

The active treatment period for cancer ("window period") was determined by independent review of the patient's anticoagulation record by two investigators (AJR, EMH), each blinded to the INR data. INR data were censored at the time of cessation of warfarin therapy, transfer of medical care, death of the patient, or study site termination. For patients newly starting warfarin, the first 30 days of INR data were excluded to minimize the variability attributable to the initiation phase. Warfarin interruptions were quantified and divided into two categories: procedure or bleeding/missed dose.

Identification of Control Patients

Each case was matched to three randomly selected control patients without cancer. Controls were drawn from the same study site as the case and were matched on age within 5 years. We excluded potential controls if they had less time in the database than the corresponding case; the window period for each control was, by definition, precisely the same number of days in length for each case and its matched controls. Patients with an INR target range encompassing values below 2.0 or

above 3.5 were also excluded. For two of the case-patients, only two eligible controls were available. For patients who were new to warfarin therapy, we excluded their INR data until they had been on warfarin for 30 days.

Outcomes

Primary outcomes included proportion of time spent in the therapeutic range and variability in the INR measurements during the window period. Secondary outcomes included major hemorrhage and thromboembolic events during the window period. Major hemorrhage was defined as a fatal event, an event requiring hospitalization with transfusion of at least two units of packed red blood cells or bleeding involving a critical anatomical site such as the cranium or the retroperitoneum.

Statistical Analysis

All analyses were performed using the SAS statistical system, version 9.1 (SAS Institute). To assess significance of effects when comparing categorical variables with the matched design, we used Monte Carlo permutation methods with 10,000 iterations to compute empirical *P* values. Case-control status within each "cluster" of matched observations was randomly permuted 10,000 times, with a test statistic (e.g., Pearson's chi-squared statistic) calculated upon each iteration. This was used as a reference distribution, under the null hypothesis of no association with case status, to compute the empirical *P* value. Groups were compared on continuous variables using a generalized linear model (PROC GENMOD) to account for correlation between each case and its matched controls.

We used three methods to compare INR values between the case and control groups. First, we compared the proportion of INR measurements in the following ranges: <2 , 2.0–3.0, 3.1–4.0, and >4.0 , using a chi-square test. Second, we used the method described by Rosendaal, et al.¹⁷ to compare the proportion of time spent within the INR target range. The Rosendaal method uses linear interpolation to impute INR values for days between measurements. INR values are not interpolated for gaps of greater than 56 days between measurements. A linear model was used to compare the mean proportion of time spent within the INR range between the two groups during the window period, accounting for matching.

We compared the variability in INR between groups during the window period, using the method described by Fihn, et al.^{18,19} This method calculates the standard deviation of INR measurements over time for each patient as a measure of variability. These data were log-transformed before comparison to accommodate the distributional requirements of the linear model. Figure 1 illustrates the concept of INR variability using the INR values of two patients from our sample; sigma is the standard deviation.

We used the Monte Carlo method described above to compare the number of thromboembolic events between the two groups during the window period. In addition, we constructed a multi-variable linear regression model to investigate the determinants of INR variability among the patients in the cancer group.

Additional Analyses

We recognize that the literature has already shown that the use of warfarin is problematic in cancer patients with VTE.^{5,11–13}

Figure 1. Graphic depiction of INR control in a patient with very low INR variability and a patient with very high INR variability.

Therefore, we were concerned that any differences between the cancer and control groups might be driven by the subset of patients anticoagulated for VTE. We addressed this concern by creating an additional, smaller dataset, composed only of the cases anticoagulated for non-VTE indications and matched controls who were also anticoagulated for non-VTE indications. We repeated our analyses using this smaller dataset; the results obtained using both datasets are presented side by side for comparison.

Study Approval and Funding

The study protocol was approved by Western Institutional Review Board® (WIRB®) of Olympia, WA and by local review boards where they existed. The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the study for publication.

RESULTS

Of the 6,761 patients, 127 patients were identified as being actively treated for cancer. Of these 127 patients, 95 met the inclusion criteria, and 32 were excluded (17—Surgery alone, 10—less than 30 days of data, 3—INR target range inappropriate, 2—transferred warfarin management to their oncologist). These 95 patients were matched to 283 randomly selected control patients. Of these 95 patients, 65 were anticoagulated for non-VTE indications; those 65 patients were matched to 193 control patients and were also anticoagulated for non-VTE indications to create our smaller, secondary dataset.

The baseline characteristics of the case and control groups from the larger dataset are detailed in Table 1. The two groups were similar in terms of age, gender, ethnicity, target INR range, and mean weekly warfarin dose. Although there was a statistically significant difference in the total amount of follow-up time in the overall cohort per patient (10.9 vs 13.1 months), the size of this difference was small. The median window periods in the cases and controls, corresponding to the period of active cancer therapy in the case patients, were 6.4 and

6.3 months long, respectively. The cancer patients were more likely than the control patients to be on warfarin due to a venous thrombotic event (31 vs 13%) and to have had more INR measurements per patient-month during the window period (2.41 vs 1.46).

In the cancer group, there were 0.16 interruptions of warfarin therapy for a procedure per patient-month, versus 0.04 in the controls ($P < .001$). The majority of patients with any procedure interruptions had only one such episode: 64% in the

Table 1. Baseline Characteristics in the Two Groups*

Characteristic	Cancer group (n=95)	Control group (n=283)	P value
Age (year)	73.5±8.95	73.3±8.71	.23
Sex (%)			.80
Male	51 (54%)	164 (58%)	
Female	44 (46%)	119 (42%)	
Race or ethnic group (%)			.95
Non-Hispanic white	87 (92%)	261 (92%)	
Non-Hispanic black	2 (2%)	6 (2%)	
Hispanic	3 (3%)	5 (2%)	
Other	3 (3%)	11 (4%)	
Target INR range (%)			.14
2.0–3.0	87 (92%)	246 (87%)	
2.5–3.5	8 (8%)	37 (13%)	
Mean time from first INR to last INR, months	10.9	13.1	<.001
Mean weekly warfarin dose, mg	30.97	30.14	.63
Mean frequency of INR measurements per 30 days	2.41	1.46	<.001
Mean interruptions of warfarin per patient-month			
Interruptions for procedures	0.16	0.04	<.001
Interruptions for bleeding or missed dose	0.07	0.05	.18
Indication for warfarin (%)			<.001
Atrial fibrillation	42 (44%)	155 (55%)	
Venous thromboembolism	29 (31%)	39 (13%)	
Prosthetic heart valve	13 (14%)	34 (12%)	
Stroke	9 (10%)	28 (10%)	
Other	2 (2%)	26 (9%)	
Incident cancer†	51 (54%)	NA	NA
Type of Cancer			
Prostate	20 (21%)	NA	NA
Breast	18 (19%)	NA	NA
Lung	8 (8%)	NA	NA
Blood-Borne (Myeloma, Leukemia, Lymphoma)	7 (7%)	NA	NA
Colon	6 (6%)	NA	NA
Bladder	3 (3%)	NA	NA
Liver	2 (2%)	NA	NA
Sarcoma	2 (2%)	NA	NA
Esophagus	1 (1%)	NA	NA
Kidney	1 (1%)	NA	NA
Melanoma	1 (1%)	NA	NA
Could not be determined by chart review	26 (27%)	NA	NA
Treatment received for cancer‡			
Surgery	24 (26%)	NA	NA
Chemotherapy	47 (49%)	NA	NA
Radiation therapy	31 (33%)	NA	NA
Hormonal therapy	21 (22%)	NA	NA
Palliative therapy	9 (10%)	NA	NA

*INR International Normalized Ratio, NA not applicable

†Cancer diagnosis occurred after patient's enrollment in the cohort.

‡Treatment received for cancer percentages do not total 100% due to multiple therapies in some patients.

Table 2. Comparison of INR Control, Major Bleeding Events, and Thromboembolic Events

Parameters	Includes patients with VTE			Does not include patients with VTE		
	Cancer group (n=95)	Control group (n=283)	P value	Cancer group (n=65)	Control group (n=193)	P value
Frequency of INR by category (%)			<0.001			<.001
1.9 or less	406 (27%)	511 (19%)		234 (25%)	366 (19%)	
2.0–3.0	765 (51%)	1680 (61%)		481 (52%)	1153 (62%)	
3.1–4.0	214 (14%)	423 (15%)		126 (14%)	280 (15%)	
4.1 or more	128 (8%)	123 (5%)		85 (9%)	70 (4%)	
Interpolated time in INR range (Rosendaal method)						
Below target range	26% (23–30%)	19% (16–22%)	<0.001	26% (22–31%)	19% (16–21%)	.003
Within target range	54% (49–58%)	66% (64–69%)	<0.001	54% (48–59%)	69% (66–72%)	<.001
Above target range	20% (16–23%)	15% (12–17%)	0.02	20% (16–25%)	12% (10–15%)	.002
INR variability (Fihn method)						
Mean INR in each group	2.54 (2.45–2.64)	2.55 (2.49–2.60)	0.94	2.59 (2.49–2.71)	2.51 (2.45–2.56)	.13
Standard deviation in each group	1.31 (0.99–1.63)	0.71 (0.54–0.89)	<0.001	1.23 (0.95–1.52)	0.64 (0.48–0.81)	<.001
major bleeding events	1	0	0.25	0	0	NA
Thrombotic events	5	0	<0.001	4	0	.005

Ranges in parentheses are 95% confidence intervals. The 95-case group includes patients with VTE, the 65-case group does not.

NA Not applicable

cancer group and 81% among the controls. Brief interruptions of warfarin therapy for minor bleeding episodes or missed doses were similar between the two groups (0.07 vs 0.05 interruptions per patient-month, $P=.18$).

Analysis of INR Control and INR Variability

Table 2 shows a comparison of measures of INR control between groups. The mean INR values achieved in the two groups were nearly identical (2.54 and 2.55). However, the cancer group had greater INR variability (SD 1.31 vs 0.71, $P<.001$), spent proportionately less time in the therapeutic range (54 vs 66%, $P<.001$), and more time above (20 vs 15%, $P=.02$) and below (26 vs 19%, $P<.001$) the target range. These results were nearly identical when the analyses were repeated with the non-VTE dataset.

In the multivariable analysis of determinants of INR variability in the cancer group (Table 3), the receipt of chemotherapy and any interruption of warfarin therapy for a procedure were significantly associated with increased INR variability (2.0- and 1.4-fold increases, respectively). Older patients did not have especially high variability. The receipt of radiation therapy and hormonal therapy did not predict increased INR variability. Interrupting warfarin therapy due to a bleeding

event, rather than for a procedure, did not predict increased INR variability. Again, these results were nearly identical when the VTE patients were excluded.

Thrombotic Events and Major Bleeding Events

Within the window period, 5 of the 95 patients (5.3%) in the cancer group sustained a thromboembolic event; 4 of these occurred among patients taking warfarin for atrial fibrillation (2 strokes and 2 pulmonary emboli) and another pulmonary embolus occurred in a patient with a prior deep venous thrombosis. For four of these patients, the event occurred during a period of warfarin interruption. No patient in the control group experienced a thromboembolism during the window period ($P<.001$ for a difference between groups). In the non-VTE dataset, there were four thrombotic events among the cases and none among the controls ($P=.005$). Three of these four events occurred during a period of warfarin interruption.

Major bleeding occurred in one case-patient with VTE (subdural bleed during bridging therapy with low molecular weight heparin). Another case-patient (non-VTE) was hospitalized with an acute gastrointestinal hemorrhage and was taken

Table 3. Multivariable Model to Predict INR Variability in the Cancer Patients

Parameters	Includes patients with VTE			Does not include patients with VTE		
	Beta coefficient	95% CI	P value	Beta coefficient	95% CI	P value
Female gender	0.057	(−0.24–0.35)	.70	0.188	(−0.14–0.51)	.25
Age ≥ 75	0.088	(−0.21–0.39)	.57	0.209	(−0.12–0.54)	.21
Chemotherapy	0.713	(0.37–1.06)	<.001	0.784	(−0.41–1.15)	<.001
Radiation therapy	−0.102	(−0.43–0.22)	.54	−0.274	(−0.60–0.06)	.10
Hormonal therapy	0.058	(−0.32–0.44)	.77	−0.195	(−0.61–0.22)	.36
Any procedure interruptions (dichotomous)	0.340	(0.03–0.65)	.03	0.363	(0.04–0.69)	.03
Any bleeding interruptions (dichotomous)	0.105	(−0.22–0.42)	0.52	0.124	(−0.24–0.49)	.51

The R^2 for the model was .20 with the larger group and .35 with the smaller group. The effect sizes for chemotherapy and any procedure interruptions are 2.0- and 1.4-fold increases in variability in both models.

The model results on the left include the VTE patients ($n=95$), while those on the right exclude those patients ($n=65$). Boldfaced variables are significant at the .05 level.

off warfarin, but we were unable to validate the number of packed cell transfusions. No bleeding occurred among the control patients.

DISCUSSION

In this community-based cohort of patients receiving warfarin for varied indications, we found that patients with an active malignancy spent less time in their target INR ranges, had more variable INR values, received more frequent INR testing, and experienced more thrombotic events than patients without a malignancy. When we repeated our analyses after excluding patients anticoagulated for VTE, these results remained essentially unchanged. This suggests that the use of warfarin in cancer patients is challenging, regardless of the indication for anticoagulation.

While other investigational and observational studies have investigated the treatment of VTE in cancer patients,^{5,11,13,20,21} to our knowledge, none have examined the effectiveness of warfarin for non-VTE indications. In our study, 69% of cancer patients were on chronic warfarin therapy for indications other than VTE, and four of the five thrombotic events in the cancer group occurred in patients who were anticoagulated for atrial fibrillation. Of the five thromboembolic events in the cancer group, four occurred during a period of warfarin interruption, which emphasizes the importance of this factor in the difficulty of managing warfarin in cancer patients. We also found an association between the receipt of chemotherapy and increased INR variability in the cancer group, which is consistent with prior observations.^{2-8,22-24}

The INR control achieved among our noncancer group, 66% time-in-range, is similar to that reported for patients enrolled in randomized trials (66.4%) and anticoagulation clinics (65.5%).²⁵ Because our control patients were matched to the site of the case, the 54% time-in-range of the cancer patients further highlights the difficulties in warfarin management for this patient group. In a similar study, Palareti et al.⁵ identified 95 patients with cancer from within a large, Italian population-based cohort study of patients receiving an oral vitamin K antagonist for treatment of VTE. The outcomes for these 95 patients were compared to the outcomes of 733 patients without cancer. The investigators found that the cancer patients had higher rates of major bleeding (5.4 vs 0.9%) and a trend toward higher rates of thrombotic complications (6.8 vs 2.5%, $P=.058$). In their study, cancer patients also spent a greater proportion of time above the target INR range (8.8 vs 4.5%), although this difference was not statistically significant.

Some limitations of our study should be noted. Despite the robust size of the overall cohort, we only identified 95 patients with an active cancer. Our identification of case-patients was contingent on the quality of documentation in the anticoagulation clinical notes. However, because the diagnosis and treatment of cancer would be so germane to warfarin therapy, we feel confident that the notes would have documented such information. Because signed informed consent was necessary to participate, we may have selected for a healthier group of patients. This would be expected to bias toward the null, suggesting that our findings may be an underestimate of the effect of cancer on anticoagulation.

Our study has several important strengths. The omission of the first 30 days of warfarin therapy excluded a potential source of bias due to INR variability during the initiation of therapy. The overall cohort was representative of the wide variety of patients treated with warfarin in the community. A manual review of every clinical record in the database minimized the likelihood of missed clinical events or assignment bias. Our study used a careful matching procedure to minimize between-group variability relating to site of care, age, and overall observation time on warfarin. Finally, our additional analysis, performed only among patients without VTE, excludes the possibility that the patients with VTE are driving our observed differences.

Because chemotherapy is such a potent risk factor for INR fluctuation, patients and providers need to be particularly vigilant during these periods to minimize the variability induced by exogenous factors such as known potentiating medications. Consistent dietary intake of vitamin-K rich foods may help to offset fluctuations in INR in patients prone to erratic control.^{26,27} Risks and benefits associated with bridging therapy during periods of warfarin interruption need to be better defined in this patient population. Newer anticoagulant drugs with a wider therapeutic index and less potential for medication and dietary interactions will hopefully translate into improved effectiveness of anticoagulation for the prevention and treatment of thromboembolism among patients with malignancy.

In conclusion, we found that in a community setting, cancer patients receiving warfarin for diverse indications had more erratic control of their anticoagulation than matched controls without cancer. They also had a significantly increased rate of thrombotic complications. Among the cancer patients, the receipt of chemotherapy was associated with increased INR variability. When we repeated our analyses after excluding VTE patients, these findings were essentially unchanged, suggesting that the difficulty of managing warfarin in cancer patients is not limited to those with VTE. Our findings extend the results of previous studies regarding the treatment of VTE in cancer patients and suggest that warfarin may not be the optimal anticoagulant for cancer patients for any indication, especially during treatment with chemotherapy.

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