

Short Communication

Predictors of Inactivation and Reasons for Participant Inactivation during a Skin Cancer Chemoprevention Study¹

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Abstract

Maintaining good compliance is a major challenge in long-term cancer chemoprevention trials. Minimizing the number of inactive participants during a trial is an important factor in maximizing compliance. Identifying reasons for and predictors of inactivation is the first step in being able to reduce participant inactivation. In this skin cancer chemoprevention trial, the 2,297 participants were randomized to receive 25,000 IU of retinol daily or a placebo. Median follow-up time was 3.8 years. The reason for inactivation was determined for each participant who stopped taking the study capsules. Six hundred and seventy-seven (29.7%) participants became inactive during the 5-year study. There was no significant difference between the number of participants inactivating by treatment group or sex. The most common reasons for inactivation were illness of subject, spouse, or a close relative (18.6%) and experience of a clinical symptom consistent with vitamin A ingestion (17.1%). Participants in the vitamin A group (10.1%) more frequently cited symptoms coded as “not consistent with vitamin A” as the reason for inactivation compared with those in the placebo group [5.4% ($P < 0.05$)]. The inactivation rate was highest in the first month of the trial and declined thereafter. A low education level (hazard ratio, 1.59) and unmarried status (hazard ratio, 1.29) were the only significant predictors of inactivation. These findings may be useful in developing targeted strategies to decrease inactivation and thereby increase compliance in future chemoprevention trials. However, these findings need to be confirmed because published research in this area is very limited.

Introduction

One of the major goals in a chemoprevention trial is maintaining good compliance with the study regimen throughout the trial. Once participant accrual has been achieved, the power of a trial is dependent on participant compliance with the study

regimen. In large part, good compliance is achieved by keeping participants active in the study because by definition, once a participant becomes inactive, their compliance becomes zero. The term “inactive” has been used instead of the traditional word “dropout” because dropout infers that a participant had no further involvement in a study, whereas those who become inactive continue to be followed periodically for ascertainment of the study end point. Minimizing the number of participants who become inactive is of great importance to researchers in this area.

Chemoprevention trials are generally of long duration and require large numbers of participants; any benefit is not measurable by the individual. All of these factors are likely to reduce compliance with the study regimen. When large numbers of participants are involved in a trial, it is very expensive and difficult to give the individualized attention to each participant that might enhance compliance. Data from treatment trials show that when a participant does not perceive that the intervention is beneficial to them, they are less likely to remain active (1).

Few published reports have evaluated the reasons for inactivation or predictors of inactivation in prevention trials. In the CARET³ Phase II pilot studies, significant predictors of inactivation for the asbestos-exposed participants were being nonwhite, having a history of high blood pressure, having higher baseline levels of negative mental health (*i.e.*, anxiety, depression, and fatigue), and reporting of specific symptoms during the placebo run-in period (2). In the smoker participants, the reporting of symptoms during the placebo run-in period was the only significant predictor of inactivation (2). Participants in these trials were at high risk for lung cancer but otherwise healthy. The most common reasons for inactivation in both pilot studies were general health issues and reported monitored symptoms that were seen as specific to the CARET vitamins. In a study of the outcomes of a placebo run-in period in a head and neck cancer chemoprevention trial, the authors reported that 35 of 391 former cancer patients were not randomized after a placebo run-in period (3), mainly due to loss of interest in participation ($n = 20$). A Karnofsky score of 100 and at least a high school education were significant predictors of randomization after the placebo run-in phase. Lower compliance in treatment regimens has been found to be associated with low educational levels, complexity of the regimen, and frequency of side effects and symptoms (4, 5). Some studies have found lower compliance associated with increasing age, but this is not a consistent finding (4).

Reasons for inactivation are of importance to researchers for at least two reasons. Firstly, an imbalance in inactivation rates between treatment arms for a specific reason may indicate that the intervention is having detrimental effects. Generally,

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³ The abbreviations used are: CARET, Carotene and Retinol Efficacy Trial; HR, hazard ratio; CI, confidence interval.

anticipated adverse effects would be detected by routine monitoring. However, subtler detrimental effects, such as a change in some aspect of quality of life, may only be detected through the monitoring of inactivation rates and reasons for inactivation. Secondly, monitoring of the reasons for inactivation may afford the opportunity to address some of the reasons while the trial is ongoing. Identifying predictors of inactivation could allow a group of participants to be targeted to receive enhanced support to maintain their active status and thus decrease the ultimate inactivation rate.

Describing predictors of inactivation may also be useful for future studies. With such knowledge, researchers could, if appropriate, exclude individuals at greater risk of becoming inactive or preferably offer greater support to them once enrolled in a trial. In this study, the reasons for participants becoming inactive while enrolled in a large skin cancer chemoprevention study are described. Characteristics of participants who became inactive are also discussed.

Materials and Methods

Trial Design. A total of 2,297 participants who had at least 10 clinically diagnosed actinic keratoses were randomized to receive either 25,000 IU of vitamin A (retinol) daily or a placebo. If eligible, participants were randomized to the trial after a 3-month placebo run-in period. Eligibility criteria included a 75% or greater compliance rate during the run-in period as measured by capsule count. The study, conducted at the University of Arizona Cancer Center, was approved by the University of Arizona Human Subjects Committee, and informed written consent was obtained from all participants. The details of the trial design and results have been described elsewhere (6–8).

Demographic information and other baseline information were collected by use of a self-administered questionnaire at the enrollment visit. Participants were seen 1 month after their randomization visit and semiannually thereafter. At each visit, participants were asked specifically if they had experienced specific symptoms and/or health problems (8). When a participant reported a symptom or sign classified as possibly related to vitamin A ingestion, the interviewer categorized the severity using standardized definitions. A set protocol was used to determine whether dose reduction or cessation of the capsules was necessary (8) to assess the association between the symptom and the intervention.

Blood parameters were assessed at enrollment (3 months before randomization), at 1 month after randomization, and annually thereafter. Dose modification, following a set protocol, was used if any of the prespecified safety criteria were met (8).

A participant was defined as inactive if he/she discontinued the study capsules permanently. Accommodation was made where possible to maintain a participant's active status; when necessary, a participant could permanently reduce their dose or temporarily discontinue their study capsules and still remain active. For example, a participant who reported a symptom deemed "not associated with vitamin A," such as stomach pains, could stop and start the capsules to see if their symptom was associated with taking the capsules without becoming inactive. However, if the participant decided to stop taking the capsules, the participant was inactivated.

When a participant became inactive, the reason for his/her inactivation was categorized by the interviewer into one of four categories: (a) participant had a symptom consistent with vitamin A; (b) participant had a symptom that was not consistent

Table 1 Reasons for subjects becoming inactive

Reason	Vitamin A N (%)	Placebo N (%)	P
Abnormal blood parameter	29 (8.4)	35 (10.6)	0.33
Clinical symptom	60 (17.3)	56 (16.9)	0.88
Both clinical symptom and abnormal blood parameter	1 (0.3)	3 (0.9)	0.29
Symptoms not consistent with vitamin A	35 (10.1)	18 (5.4)	0.02
Illness of subject, spouse, or close relative	60 (17.3)	66 (19.9)	0.38
Participant moved out of the locality of the study center	18 (5.2)	17 (5.1)	0.99
Too busy or lost interest	30 (8.6)	17 (5.1)	0.07
Lost to follow-up	17 (5.9)	15 (4.5)	0.81
Fulfilled commitment to study	18 (5.9)	26 (7.6)	0.16
Fear of possible side effects from intervention	10 (2.9)	12 (3.6)	0.59
Other	68 (19.6)	66 (19.9)	0.93
Total	346	331	

with vitamin A; (c) participant not willing to continue; or (d) participant lost to follow-up. A symptom consistent with vitamin A toxicity was defined as being one of the 14 clinical symptoms or one of the specified laboratory assessments that were being monitored during the trial. The interviewer recorded a narrative describing the reason for inactivation at the time of inactivation. Only one reason for inactivation was coded for each participant. When more than one reason was given for inactivation, the interviewer asked further questions to determine which of the multiple reasons was the foremost reason for the participant's inactivation. The exception to this was when a participant stated that a symptom consistent with vitamin A was one of the reasons for their inactivation; in this case, "symptom consistent with vitamin A" was the reason coded. At the end of the study, the reasons for inactivation were reviewed by one of the authors (B. C.) and further categorized as shown in Table 1.

Statistical Analysis. The χ^2 test was used to analyze the reason for inactivation as reported by participants at the time of discontinuation of the capsules, and Cox proportional hazards analysis was used to analyze baseline predictors of inactivation. Fifteen of the 2297 randomized participants were determined to be ineligible for the study after being randomized. These participants were asked to stop taking the capsules when they were determined ineligible and are not included in the analysis. Active participants who died were censored at date of death. All other active participants were censored at their last contact date. The date of last contact was used as the date of inactivation for participants who were classified as lost to follow-up ($n = 32$). The analysis investigating predictors of inactivation was conducted both including and excluding participants who were directed by the study staff to stop taking the study capsules due to symptoms associated with vitamin A.

Results

A total of 677 (29.7%) participants became inactive during the study (30.1% in the vitamin A group and 29.2% in the placebo group). There was no difference in the proportion of participants who became inactive by treatment group.

The reasons for inactivation by treatment arm are shown in Table 1. Examples of illnesses of the subject, spouse, or a close relative are cancer, stroke, and fractures. Symptoms coded as not consistent with vitamin A, such as dizziness, stomach pains, and diarrhea, were cited as the reason for inactivation more frequently by participants in the vitamin A group (10.1%) than

