CASE 15

Stopping the Carotene and Retinol Efficacy Trial: The Viewpoint of the Safety and Endpoint Monitoring Committee

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ABSTRACT

We describe our experience with the events that occurred when it began to be suspected that beta-carotene in non-physiological doses had an unexpected adverse effect on the incidence and mortality from lung cancer. Initially, we delayed a decision to recommend stopping the Carotene and Retinol Efficacy Trial (CARET) for a year, until we were convinced that an adverse trend seen in the first interim analysis of the trial persisted. In hindsight, this seems to have been the correct decision.

INTRODUCTION AND BACKGROUND

The hypothesis that ingestion of beta-carotene was protective for lung cancer arose from a series of observational epidemiology studies, both case-control and cohort (reviewed in IARC).[1] Although there was a possibility that consumption of beta-carotene was an index for a diet high in beta-carotene-containing foods, and that the protective effect was due to other substances in plant foods, it was felt important that the putative protective effect should be assessed by randomized intervention trials in humans. Therefore, in the 1980s, a series of trials were designed to assess the beta-carotene hypothesis.

[†] Dr. Frank Iber was also a member of the SEMC during the events described in this paper, but could not be reached by the first author and therefore had no opportunity to participate in the preparation of this manuscript.

The Carotene and Retinol Efficacy Trial (CARET) was funded in July 1988 to determine the efficacy of a daily combination of 30 mg beta-carotene and 25,000 IU retinal (as retinyl palmitate) in preventing lung cancer in high-risk populations. These populations were heavy smokers and asbestos-exposed workers. The asbestos-exposed workers eligible were men aged 45–69, who were current smokers or quit within 15 years of enrollment, and who had their first exposure to asbestos on the job at least 15 years prior to enrollment. The heavy smokers were men and women aged 50–69 with at least 20 pack-years of cigarette smoking, and who were current smokers or had quit within the previous six years.

CARET was a multi-center trial based on two pilot studies that commenced in Seattle in 1985, one of heavy smokers (N = 1,029), and the other of asbestos-exposed workers (N = 816). These initial entrants were retained in the trial as the Vanguard cohort, who were evaluated more intensively for potential side-effects of the treatment regimen than the participants in the main trial. In the main trial, recruitment continued in Seattle, and centers were opened in Baltimore, New Haven, Portland and San Francisco that recruited asbestos-exposed workers, and the center in Portland recruited heavy smokers, as did another center in Irvine. Each center only entered the trial after their participation had been approved by their relevant Institutional Review Board. Accrual to the trial was completed in September 1994.

DATA MONITORING EXPERIENCE

The Safety and Endpoint Monitoring Committee (SEMC) was established early in the course of the main trial to act as an independent advisor to the investigators and the National Cancer Institute on all aspects of the conduct of the trial. Our mandate was largely ethical; we were initially primarily concerned with the potential toxicity of the regimens, both in the short and long term. For example, given some concerns that the incidence of prostate cancer might be adversely affected by the regimen, we early on instructed the investigators to provide us with regular data on the incidence of prostate cancer, as well as the primary endpoint of the trial, lung cancer. We met on a semi-annual basis, and were provided with coded data (i.e., masked as to regimen). We decided to use the O'Brien–Fleming[2] multiple testing procedure for clinical trials, to facilitate decisions relating to a possible early cessation of the trial, as well as the time when results would be reported. The SEMC initially had five members—two epidemiologists expert in clinical trials, a biostatistician, an expert on the pharmacology of the agents used, and a basic science researcher. After a few years, the last resigned and was not replaced. The SEMC met together with the principal investigator and stat-

istician to the trial, and representatives of the NCI, but none of these had voting rights within the committee, and when judged necessary, the committee met in executive session without them.

In practice, the SEMC encountered few problems, our regular meetings continued over the years, we were provided with all the information we requested, and we received copies of the semi-annual reports provided by the investigators to NCI. Overall, we were very knowledgeable as to the progress of the trial.

Circumstances Surrounding the Stopping of the Trial Regimens

The investigators have already published details of the cessation of the trial from their perspective, especially concentrating on the administrative issues involved.[3] Here, we provide our perspective, a perspective largely influenced by our ethical responsibilities, but also influenced by the wider aspects of science that concerned us at the time.

In April 1994, the Chairman of the SEMC had a call from NCI requesting his participation in a conference call that also include the CARET principal investigator, the director of the supporting NCI Division, and an external expert in epidemiology who was not a member of the SEMC, but who had been extensively involved in the theoretical discussions that eventually led to the trials initiation. We were informed that the initial results of the Finnish Alpha-Tocopherol Beta Carotene (ATBC) trial were about to be published.[4] This showed an unexpected significant increase in the incidence of lung cancer, rather than the protective effect anticipated. Lung cancer mortality was consistent with the lung cancer incidence. We agreed that although the regimens evaluated in CARET and the ATBC trial were not the same, the overlap in both with the use of beta-carotene made it essential that there should be an immediate review of the current status of CARET. An urgent meeting of the SEMC was called, and we requested the investigators and the statistical center to immediately proceed with an analysis of the CARET outcome data, which in effect meant the advance of the first intermediate analysis already planned for the fall of that year. The investigators and statistical center worked extremely hard, so that we were able to meet again in August 1994. We were surprised that there was a significant difference between the regimens, and although the excess incidence of lung cancer did not cross the pre-specified O'Brien–Fleming early-stopping boundary, we unanimously agreed that we should be unblinded as to the nature of the regimens given to the coded groups. We then learned than CARET was the second trial to show an increase in incidence of lung cancer following the use of a regimen including a high (pharmacologic) dose of beta-carotene.

Our decision to recommend to NCI that the trial regimen should be stopped (but that the follow-up continue) was not immediate. Indeed, there was initially a considerable difference of opinion within the SEMC. When we eventually decided to take a vote at that meeting, we were evenly divided, and the chair decided not to use his casting vote, because of the validity of the contrasting views held.

These views may be summarized as follows. In favor of not stopping the trial:

- The statistical significance of the difference had not crossed the O'Brien–Fleming boundary (i.e., this could still be a chance finding).
- The effect was surprisingly rapid and must mean if real that pre-existing (but undiagnosed) lung cancers had had their growth accelerated by the regimen.
- We knew of no mechanism of the action of beta-carotene that could have induced such an effect.
- There were other chemoprevention trials using beta carotene ongoing, to stop CARET now would have an undesirable adverse effect on these trials.
- We owed it to science to be absolutely certain of the adverse effect before stopping the trial.

In favor of immediately stopping the trial the following views were expressed:

- This was the second trial to show an adverse effect of beta-carotene chemoprevention; it was extremely unlikely to be due to chance.
- We owed it to the participants to prevent possible further harm to them. It was perhaps particularly unfortunate that the adverse effect appeared to be present in asbestos workers as well as current smokers.
- The adverse effects appeared not to be restricted to lung cancer; there appeared to be an adverse effect on cardiovascular disease as well.

Given the lack of agreement among the SEMC, it was agreed that the following actions were required:

1. The outcome events should be allowed to continue to accumulate for another 6 months; it would then be possible to determine if an apparent adverse effect was continuing.
2. The statistical center was requested to compute the possibility that if the excess of lung cancer in the active treatment arm ceased to occur, a benefit might eventually occur that could be detected given the size of the population in the trial.

3. To allow time for the additional endpoints to be determined, we decided that a second interim analysis would be performed in June 1995, and that we would meet again as soon as possible to review the status of the trial.

We recognized that this meant that we had effectively postponed a decision to stop the trial (if we then decided that was necessary) for more than a year after the ATBC results were released. However, we knew that very shortly after the publication of the ATBC results, the principal investigator had written to all CARET participants informing them of the ATBC results and reminding them of their right to stop the trial medication immediately if they were concerned.

We met again in September 1995. At that time it was clear that the excess of lung cancer had continued to accumulate in the intervention regimen at about the same rate during the time since the first interim analysis. Further, the cardiovascular disease excess persisted. The conditional power calculations showed that it was extremely unlikely that the trial could show a beneficial effect of the intervention, even if the adverse effect ceased to occur and a delayed protective effect began to appear. Therefore the SEMC voted unanimously to recommend to NCI that the trial regimen should be stopped but the follow-up should continue.

NCI decided, given the importance of the decision, that it would convene an *ad hoc* group of three biostatistician advisors, with the principal task of reviewing the biostatistical aspects related to our recommendation to them. All three were experienced with cancer trials and one had been on the data monitoring board for the ATBC trial. The *ad hoc* group reviewed the most recent SEMC report for the CARET trial as well as the published results of the ATBC trial. This group concurred with our recommendation, and the steering committee of the trial voted unanimously to terminate the trial regimen in January 1996.

LESSONS LEARNED

Taking a decision to stop a major trial is difficult, and there is no question that having done so for CARET has had a major impact on the perception of the potential value of chemoprevention for cancer. However, the research which followed fairly soon led to the elucidation of a possible mechanism for the adverse effect,[1] and this in itself has advanced the field.

The ethical aspects related to participant safety have to be paramount for a Safety and Endpoint Monitoring committee. However, ethical issues are perceived differently by different individuals, and the initial disagreement within

our committee effectively demonstrated this. Even though the relative lung cancer risk was increased, the absolute risk of an adverse effect was small, and this influenced some committee members more than others. Further, the adverse effect did not at that time seem to have a rational biological basis; thus it was relatively easy to assume that some sort of bias had created what we were seeing. It was also relevant that one of our members was an investigator in the Physicians Health Trial,[5] and it was known to her that no adverse effect of beta-carotene had so far been seen in that trial. However, there was a much smaller proportion of smokers in that trial than the ATBC and CARET trials, and we knew that the adverse effect in CARET was seen in smokers, rather than non-smokers, while ATBC had only enrolled smokers. Nevertheless, for some time, in personal discussions with the chair of the committee, the external expert that had participated in the April 1994 teleconference maintained that our eventual decision to stop the trial regimen was completely unjustified. He maintained that there was still a possibility that the adverse effect was due to chance, and that it was critical to ensure that the possibility of a protective effect from beta-carotene was not due to chance.

In practice, two circumstances made it possible for the committee members that had initially not favored the trial regimen is being stopped to change their mind. One was the continuation of the accumulation of excess adverse events in the active intervention arm between the two interim analyses. The other was the apparent impossibility of the trial's showing a beneficial effect even if this began to appear. In practice by the time the decision to terminate the trial regimen was taken, about half of the anticipated endpoints had already occurred.

Bowen et al.[3] have documented the processes the investigators had to go through to inform the participants of the decision to terminate the trial regimen in a manner that did not cause undue alarm among them. The approaches they adopted seem to have been very successful, a reflection of the fact that the initial informed consent process had imparted the necessary information that an experimental regimen was being evaluated. The importance of an even-handed approach to informed consent is highlighted by the circumstances surrounding this trial. A similar experience occurred in the Canadian trial of mammography screening which failed to demonstrate the anticipated benefit from the screen.[6] Because under the conditions of scientific equipoise needed to initiate a trial we cannot know in advance that there will either be a benefit, or even a detriment from the experimental regimen, it is in our view essential that both those allocated to the active treatment and those allocated to the control group provide informed consent. Thus what is called by some "randomized consent" (the

subjects are identified, randomized, and then those allocated to the active intervention are asked for their consent, with the controls not approached but followed through available data bases such as cancer registries and vital statistics files) is not ethically valid, as it is the right of controls to know they are being considered for a trial, and to refuse (or agree) to participate in the light of their own circumstances and beliefs about possibilities of benefit and harm.

The SEMC was blinded on a "need-to-know" basis; that is, the SEMC could choose to unblind itself when it determined it was important to know the treatment arm codes. This facilitated an unbiased approach to the first (advanced) interim analyses. Although concern with potential toxicity of a regimen (as we were in the early years of our deliberations) may result in one making inferences as to which coded arm is which, when toxicity is minimal, as it was in CARET, the placebo effect will usually result in committees remaining unblinded. This was in effect what happened during all our deliberations, until we took our unanimous decision that we should be unblinded in August 1994, when it became apparent that we needed to know whether CARET was showing early indications of a benefit from the intervention, in which case continuation of the trial to the defined endpoint was essential, or whether the adverse effect seen in ATBC had been replicated in CARET.

There seems little doubt now, with the benefit of hindsight, that we made the correct recommendation in September 1995. Also with the benefit of hindsight, given that the adverse effect has not gone away, it does not seem likely that we could have prevented many, if any, adverse events occurring if we had taken that decision one year earlier. Although the decision was delayed for a year, this has to be placed in the perspective of the state of the art of chemoprevention at that time, and the strong belief, largely derived from observational epidemiology data, that beta-carotene in physiological doses is beneficial. Indeed, reports are still appearing of diet and cancer studies that are interpreted to show a beneficial effect of such consumption. This suggests that it was the high, non-physiological doses of beta-carotene that caused the adverse effect, with unusual metabolic functions coming into play, a hypothesis that seems to be confirmed by mechanistic studies that have been performed.[1]

REFERENCES

1. IARC Handbooks on Cancer Prevention. Volume 2 Carotenoids. 1998. Lyon, International Agency for Research on Cancer.
2. O'Brien PC, Fleming TR. 1979. A multiple testing procedure for clinical trials. *Biometrics* 35:549–556.
3. Bowen DJ, Thornqvist M, Anderson K, Barnett M, Powell C, Goodman G, Omenn G. 2003. Stopping the active intervention: CARET. *Control Clin Trials* 24:39–50.

4. The Alpha-Tocopherol Beta Carotene Prevention Study Group. 1994. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 330:1029–1035.
5. Hennekens CH Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, et al. 1996. Lack of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 334:1145–1149.
6. Miller AB, To T, Baines CJ, Wall C. 2000. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women age 50–59 years. *J Natl Cancer Inst* 92:1490–1499.