The Clinical Evaluation of Cancer Chemoprevention Agents: Defining and Contrasting Phase I, II, and III Objectives

Gary E. Goodman

Swedish Hospital Tumor Institute, Fred Hutchinson Cancer Research Center, Seattle, Washington 98104

Abstract

A number of potential chemoprevention agents are now in clinical trials to evaluate their efficacy. A larger number of compounds await clinical investigation. The design of phase I and phase II trials for cancer chemoprevention agents requires a different approach than for cytotoxic agents. The unique nature of the target populations, the scope of side effect evaluation, and the potential duration of treatment must be considered in the design of these trials. This article will discuss the effect these variables have on the evaluation of a chemoprevention agent and propose models for the phase I and phase II trials of chemoprevention agents.

Introduction

Epidemiological studies have shown a correlation between the consumption of certain food groups and the incidence of cancer (1). This has led to the suggestion that naturally occurring compounds present in these foods may be responsible for the reduced cancer risk. β-Carotene, retinol, and selenium are some of the compounds thus far identified which may fulfill this role (2, 3). In addition, a number of synthetic compounds (retinoids, prostaglandin synthetase inhibitors, dimethylfluorornithine, etc.) have been shown to slow or modify the carcinogenic process in animal models (4). These findings have raised the possibility of human cancer prevention: the administration or augmentation of the dietary intake of these compounds in the hope of decreasing cancer incidence.

Before initiating trials evaluating the efficacy of a potential cancer prevention agent, it is important that the agent undergo careful clinical evaluation. In cancer prevention trials, the target populations differ significantly from populations usually participating in clinical trials. They are frequently healthy, even though they often have a higher statistical risk for developing cancer. Their motivation to participate in a trial and take an agent is different from those with diagnosed malignant disease. These unique aspects of chemoprevention call for a different approach. While there are well-established guidelines for the Phase I and II clinical evaluation of therapeutic anticancer agents, these have only limited application to chemoprevention agents. Greenwald et al. (5, 6) have proposed a schema for the phase I, II, III, and IV evaluation of chemoprevention agents. This article will discuss pertinent issues and propose a more detailed model for the phase I/II clinical evaluation of potential cancer chemoprevention agents.

Unique Aspects of Chemoprevention

There are three areas unique to the field of chemoprevention which must be considered in all stages of the clinical evaluation of a new agent. (a) the nature of the target population: for a chemoprevention agent this can imply a “well” or at least a cancer-free individual; (b) side effects: the degree and frequency of side effects which are both acceptable to the individual and medically, philosophically, and ethically justifiable in the target population differs from those in populations of “patients”; (c) duration of use: as opposed to administering treatment for a specific illness for a defined period of time, chemoprevention agents will probably have to be continued life long.

Target Population. The target populations of chemoprevention agents consist of many diverse groups. One broad division is in two populations: one consists of healthy individuals without a diagnosis of cancer; the other, a much smaller group, consists of cancer patients who are at risk for developing either recurrence or a second primary. While one may argue that this latter group is the target for “adjuvant” therapy and not “chemoprevention,” our current understanding of malignant transformation and progression suggests a continuum between these two clinical populations. The transformation of a normal cell to one with a malignant phenotype is thought to occur many (5–10) years prior to clinical diagnosis (7). This concept would, for practical purposes, make chemoprevention trials which count as failures all cancers occurring within 5–10 years of starting the chemoprevention agent, in actuality, adjuvant trials, i.e., the treatment of patients with undiagnosed microscopic cancer. This is analogous to a patient with stage II breast cancer who has had a “curative” surgical resection but who has undetectable, microscopic metastatic disease. A “true” chemoprevention trial would discount all incident cancers during the initial 5–10 years of the trial. Hence, the concept of what is meant by the term “chemoprevention” and the distinction between chemoprevention trials and adjuvant trials hinges on the tumor burden which one believes (has evidence) that an agent will modulate.

Barring these theoretical concerns, the practical differences in conducting trials between these two populations (well versus those diagnosed as having cancer) is significant. These differences can have a profound impact on recruitment, the choice of agents, and follow-up methods. The group with a diagnosis of cancer even though potentially cured fall into the realm of “patients.” They are more integrated into the medical system and are more accessible to be recruited. In addition, they are frequently motivated by their diagnosis. The well group, however, frequently has no such motivating factors and may not be easily accessible for recruitment. These groups are most correctly referred to as “participants” or “collaborators.” This latter population raises issues not addressed by current phase I, II, and III cytotoxic drug evaluation trials.

Risk and Its Perception. One of the areas in which patients and participants can differ is their perception of cancer risk. Within the well population there are individuals who are concerned about their risk for developing cancer. There are others who have no perception of this risk. There is frequently little correlation between an individual’s perceived risk and the actual or statistical risk for developing cancer. Perceived risk and not actual risk can be one of the primary motivating factors for an individual to take a chemoprevention agent or participate in a trial. Individuals with a high degree of perceived risk are likely to be highly motivated, while those with a low perception of...
risk will be easily dissuaded from both participating in a trial and taking the prevention agent. This is opposed to patient treatment programs where motivation and reinforcement to taking the prescribed agent can be buttressed by the treating physician as well as a positive result, e.g., a fall in blood pressure after the initiation of antihypertensive agents. Efficacy for a chemoprevention agent means maintenance of a cancer-free status. This may not be realized as a positive by the individual, especially if health is declining in other spheres.

The two factors of perceived risk and actual risk are useful in classifying target populations when deciding recruitment requirements and strategies for phase I and II trials. For example, individuals with a diagnosis of familial colon cancer, polyps, or dysplastic neus syndrome, have a well-defined high risk for developing malignancy. These individuals along with those having a diagnosis of cancer who are at high risk for recurrence or a second primary can be considered as “patients.” Treatment with a chemoprevention agent is medically justified; actual risk is high. These individuals are also aware of their risk factors because of their diagnosis or the familial nature of their malignancy; perceived risk is high. Hence, they have a high degree of both perceived risk and actual risk. These groups are frequent targets for phase I and II trials.

Another much larger population are those individuals who have a higher cancer risk than the general population, but who frequently have a low level of perceived risk. These groups include cigarette smokers, ethanol users, and those who may not be educated about their risk, such as families with multiple breast, ovarian, or colon cancers. Their level of perceived risk may make them harder to recruit and less willing to participate in a trial of an agent with potential side effects. When side effects occur they may be less willing to accept them. In this aspect, the choice of agent may dramatically affect adherence in these populations. Depending on the agent, they are rarely appropriate for the initial evaluation of a chemoprevention agent (phase I trial). Since these groups are ultimately where an agent may have applicability they are ideal targets for phase II and III trials. However, recruitment and retention, those features of prevention trials that are most strongly influenced by perceived risk, can be a major problem.

Recruitment to a chemoprevention trial can be dramatically different from a trial in cancer patients. The normal mechanism by which a clinician enters patients on a clinical trial is through direct patient contact. For those diagnosed with cancer and referred for treatment (“patients”), this method works well. However, for the well population (“participants”), recruitment to a clinical trial becomes more complex. This group is usually not integrated into the medical care system. In addition, if approached, they do not see themselves as ill or at high risk. Analogies to trials evaluating antihypertensive agents and antihyperlipidic agents are not valid, since both hypertension and hypercholesterolemia are recognized by the general public as diagnosed medical problems which require treatment. This tends to encourage enrollment in a “treatment” trial and adherence with the “treatment program.” No such diagnosis exists for participants in a chemoprevention trial. Those who chose to join a study are highly self-selected. The perceived risk of the individual is considered to be a primary motivating factor which determines participation in a trial. Recruitment and retention of the general public or those with a low degree of perceived risk are unique aspects of a chemoprevention trial.

Side Effects. Another unique aspect of chemoprevention agents is the scope of side effect evaluation. Most of the agents proposed as chemoprevention agents have the potential to be given for long periods of time to large populations who individually have a low risk for developing cancer (although they may be in a “high risk” group, their absolute risk is low). Any agent causing toxicity or unexpected side effects may be more of a detriment than a benefit from the public health standpoint. Thus, it becomes important to clearly define the dose/toxicity/efficacy relationship of any proposed cancer prevention agent before it can be used in large unmonitored populations.

Side effect evaluation must be sensitive to common minor side effects in addition to more serious toxicities. The occurrence of side effects, even those which are relatively minor (yet alone classified as “dose/limiting”) may rule out the potential use of an agent in all but the highest risk populations. The design and accrual goal of a trial will have to consider the number of participants needed to identify rare side effects. The evaluation of long term rare events can be particularly difficult.

The judgment of whether an agent has an unacceptable spectrum of side effects cannot be made on an absolute basis. Four factors must be considered: (a) what is the spectrum and incidence of both acute and chronic side effects; (b) what is the level of perceived risk of the target population (what degree of side effects will be acceptable); (c) what is the actual cancer risk for the population; and (d) what is the efficacy of the agent? These factors are all highly interdependent.

The spectrum of side effects acceptable to each target population will vary with their perceived risk. Acceptance will be manifested as adherence (taking the agent) and retention (remaining on the trial). For example, /-carotene, at doses of greater than 30 mg/day, frequently causes yellowing of the skin (8). This has little risk and is usually well tolerated by all populations. Another potential side effect is diarrhea. In an elderly population, which has a high incidence of chronic constipation, loose stools may be acceptable or even desirable. In a younger population it may be unacceptable. Hence, some side effects may be acceptable (desirable) in one population but not in another. The perceived risk of the individual will determine if taking the agent “is worth the bother.” The spectrum of side effects and perceived risk will be one of the factors used in determining which agents are appropriate for specific high-risk populations.

The third and fourth factors relate the actual risk of the target population and the efficacy of the agent with side effects. Agents with frequent side effects or more serious side effects may require frequent medical monitoring and treatment. Let us assume there is an agent which has good efficacy and can decrease cancer deaths by one-third. This agent is planned for use in a high-risk population which has a 0.3%/year cancer death rate. Assume the agent has a 5% incidence of side effects, and those who develop these side effects visit a physician for evaluation. One might assume that this agent would be acceptable. However, if the agent has a 25% incidence of side effects, a much larger group of previously asymptomatic individuals would be seeking medical care for iatrogenic problems. In both cases, the agent’s efficacy would decrease the death rate to 0.2%/year and would appear to be justified based on their risk reduction. However, the incidence of minor side effects and their medical management would greatly differ in terms of morbidity, health care dollars, and allocation of resources.

A clearer relationship exists between the incidence of severe side effects (life threatening) and the incidence of the underlying cancer. Assume that an agent with a 0.1%/year incidence of life-threatening side effects and 33% efficacy is to be used in a
cancer with a death rate of 0.3%/year. The potential number of deaths due to the agent would be equal to the number of cancers deaths prevented. Such an agent would have no effect on decreasing the death rate in the target population and would not be justifiable because of side effects alone. If 100% effective in preventing a cancer, a chemoprevention agent must have an incidence of life-threatening side effects less than the cancer death rate of the target population.

Duration of Therapy. The final aspect unique to chemoprevention is the expected duration of treatment. Experimental work with both in vitro cell culture systems and animal studies have shown that most chemoprevention agents with antipromotional activity must be continuously present for efficacy. If the agent is removed from the culture system or discontinued in the animal, the cancer incidence returns to the pretreatment rate (2). This suggests that chemoprevention agents will be given for prolonged periods. An issue usually not addressed in phase I/II/III studies of cytotoxic drugs is the incidence of long term side effects. In chemoprevention, where the majority of participants will live a normal life span and not develop cancer, determining the incidence of long term side effects is critical. The planning of phase I, II, and III trials must consider this aspect of chemoprevention; these agents will likely be administered for life.

Objectives for Phase I/II Trial

Like phase I and II trials of cytotoxic agents, trials of chemoprevention agents have a number of specific objectives. The three broad areas just discussed must be taken into consideration when designing trials addressing these objectives.

Side Effect Evaluation. Evaluation of side effects is a major component of phase I and II trials. Since these agents may be given to large, healthy populations, side effects must be minimal. The clinical evaluation must be sensitive to a wide spectrum of acute and chronic side effects. This evaluation contrasts strikingly with the focus on short term major side effects of chemotherapeutic agents.

It is useful to divide side effects into those which can be categorized as “major” and “minor.” While this division is artificial and subject to interpretation, it is operationally useful. Major side effects can be defined as any side effect leading to death or any life side effect which requires medical intervention, is life threatening, or causes long term disability. Examples of major side effects are bone marrow suppression, renal failure, hyper- or hypotension, and diabetes mellitus. If an agent causes major side effects during a phase I or II trial, there would be a major reevaluation of its potential as a clinically useful agent. It is unlikely that such an agent would be justifiable in most target populations.

Minor side effects are those which cause reversible events and rarely require medical intervention. These may include hair loss, nausea, skin rashes, diarrhea, headaches, etc. The incidence, severity, and spectrum of minor side effects, although not a risk to survival, will help delineate which populations are appropriate targets for its use.

Chemoprevention agents in general must have a very low incidence of major side effects but may have minor side effects. The evaluation of these minor side effects (which participants may not even associate with the agent) should consist of a standardized evaluation by physical examination and questioning for the occurrence of symptoms. As with cytotoxic drug trials, grading scales for side effects should be constructed and the participant graded at each contact. The minor nature of many potential side effects stresses the importance of assessing and recording symptoms in a standardized fashion within the context of a randomized trial.

Exploring Dose/Toxicity Relationships. A review of the preclinical dose/efficacy evaluation of an agent should be undertaken prior to the start of phase I or II clinical trials. Although it is unclear if animal or in vitro studies have predictive value in humans, these studies do give information on biological activity and the likelihood that an agent may have a dose/efficacy relationship in humans. If higher efficacy is seen with higher doses, phase I and II trials should evaluate multiple dose levels.

If in vivo and in vitro trials do not suggest a dose/efficacy relationship, there is probably little reason to evaluate multiple doses in a phase II trial and, later, phase III trial. The dose chosen for phase II evaluation should be two levels below the dose at which the first side effects occurred in the phase I trial. This is based on a philosophy of using the highest possible dose of an agent but maintaining a very low tolerance for side effects.

Retention Evaluation. The target populations for chemoprevention trials are not always easily accessible. Many phase III chemoprevention trials will require a large number of participants for statistically valid result. While the recruitment of participants to phase I or II trials may be straightforward, these trials can provide an estimation of recruitment rates from various sources and allow a forum for testing strategies to improve recruitment.

Retention Evaluation. Once recruitment is complete, retention of participants to the trial becomes a major focus. Participation requires regular self-medication (with the chemoprevention agent) as well as maintaining the required follow-up schedule (clinic visits, questionnaire completion, etc). The phase II trial offers an opportunity to estimate retention of the target population. It also allows the establishment and testing of methods to improve retention.

Exploring Dose/Efficacy Relationships: Intermediate End Points. Although phase I and II clinical trials do not usually have sufficient accrual to evaluate the cancer end point, there may be some attempt to evaluate efficacy via the study of intermediate end points (6, 9, 10). Because cancer is a statistically uncommon event (even in high risk groups) large populations and long term follow-up are required to determine the effect on cancer incidence. The concept of an intermediate end point has been introduced in an attempt to evaluate efficacy in a shorter time and with fewer subjects. These trials usually measure some cellular event as a surrogate end point for cancer. Some suggested intermediate end points are a cytological or histological change, a change in the cellular antigenic profile, the incidence of micronuclei (an indicator of nuclear chromatin damage), or a change in expression of various oncogenes or tumor suppressor genes. The objective of an intermediate end point trial is to determine if the agent being studied can change the incidence of the measured end point.

Hence, in addition to the clinical parameters (recruitment, retention, side effects) these trials may have an additional objective of determining the effect on an intermediate end point. Since there are few proven intermediate end points, those trials may involve different personnel, methods, and follow-up evaluation. We have accommodated this divergence by dividing trials into part A and B. The part A trial encompasses all the clinical parameters while the part B focuses solely on interme-
diate end points. Part B trials can be conducted during phase I, II, or III evaluations.

Phase I Trial

As with cytotoxic drugs, the phase I trial is the first clinical evaluation of an agent (Table 1). The primary objectives of this trial are to determine the incidence and spectrum of side effects which occur during the first 12 months of treatment. This trial will determine if further clinical evaluation of the agent should take place. As in the phase I evaluation of cytotoxics, standard Fibonacci dose escalation should continue until minor side effects are seen in the majority of subjects at the highest dose level. Higher dose escalation is probably not warranted, since these doses will probably not be useful in most target populations.

Since these trials recruit small numbers of participants, they provide little information on recruitment potential and retention. Intermediate end points may be studied in a phase I trial; however, due to the small population, statistically valid results may not be obtained. However, methods for an intermediate end point trial can be piloted with biological samples obtained during a phase I trial.

The smaller population recruited makes a more intensive investigation of the agent’s pharmacokinetics possible. Patients can be studied at each dose level. Specific pharmacokinetics questions such as drug distribution to target tissue and drug metabolism can also be studied during the phase I trial.

Phase I trials are single arm and should accrue 20 to 25 patients at each dose level. Participants should be enrolled at each dose level in a staggered fashion allowing weeks to pass before accruing to the next dose level. Barring major side effects the entire population (all dose levels) should be treated and followed for at least 12 months. This will allow the deletion of short term side effects (<12 months) with an incidence of 20% or greater.

The population enrolled should be determined by the known preclinical toxicity of the agent. Ideally, an agent that has a projected target tumor should be evaluated in a population at high risk for that tumor. However, agents with unknown or potentially major side effects can be justified only in patients who already have a diagnosis of cancer or those who have a high risk for relapse. Agents with a low side effect potential can be used in healthy populations having only well-defined risk factors.

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<tr>
<td><strong>Objectives</strong></td>
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<tr>
<td>Side effect</td>
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<td>Low toxicity potential: appropriate target population</td>
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<tr>
<td>Accrual goal</td>
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Phase II Trial

If the phase I evaluation of an agent proceeds without major side effects and epidemiological and laboratory studies continue to suggest efficacy, a phase II trial may be indicated. This trial will extend the finding of the phase I trial and begin to address questions which require larger enrolled populations (Table 2.)

Phase II trials are usually placebo-controlled, double-blind trials which allow a more careful evaluation of potential side effects than in a phase I trial. Many potential side effects of chemoprevention agents can commonly occur in untreated populations (i.e., headaches, diarrhea, rashes, etc.). It is important to take a standardized approach to the evaluation of these common symptoms. The difference between placebo and active treatment may only be an increase in intensity or frequency of these common symptoms.

Evaluation of symptoms may consist of a standardized physical examination and questionnaire, either self-administered or interviewer administered. These should evaluate both the degree and frequency of symptoms. Evaluation should occur at regular intervals for the duration of the trial. To describe a symptom or a laboratory abnormality as a side effect, one should document a significant difference in incidence rates between the treatment and placebo arms.

The dose of the agent should be based on laboratory studies evaluating efficacy and side effect data obtained during the phase I trial. Those agents with acceptable side effects at multiple dose levels and evidence for a dose/effect relationship warrant a multidose evaluation, especially in the phase IIB trial. Agents without a clear dose/effect relationship should probably have a single dose evaluation utilizing the highest dose free of side effects in the phase I trial.

The larger population recruited to the phase II trial makes it possible to evaluate the relative success of recruitment and retention methods. Different recruitment methods can be evaluated to determine the most successful for a future phase III trial. The success of a recruitment evaluation will vary with the size of the population accrued and the methods used to define recruitment strategies and responses.

The intermediate end point trial (part B) is an attempt at efficacy evaluation during a phase II trial. The natural history of many proposed intermediate end points has not been completely described in populations at risk. The placebo-controlled design of the phase II trials allows a description of the natural history of the marker (placebo group) as well as the effect of the intervention agent.

The accrual goal of a phase II trial is usually determined by the statistical requirements of the intermediate end point evaluation. This is driven by the desire to detect some evidence of efficacy before being overly concerned about precisely describ-
end point trial are different from those indicated for a statistical
effects between a placebo and an active agent becomes possible
allows the initial evaluation of these multiple characteristics
agent being tested, and the target population. The phase II trial
aspects of clinical operations such as rates of cancelled appoint
also estimate adherence to the study agents and other important
This includes the structure and content of the clinical interac
tumor being studied and the expected incidence and severity of
variations in population requirements. When planning accrual
other discomforts of the trial. Many phase II objectives (of a
term side effects. Hence, the occurrence of side effects is unlikely to
incidence of the side effect to be evaluated can result in wide
ment groups and the difference one wishes to detect. The
incidence of side effects related to the agent are likely to occur initially in the
Close monitoring will allow early detection of side effects, and if necessary, modification of the dose in the larger phase
more intensive monitoring of the vanguard cohort allows the phase III cohort to be less intensely monitored for side effects. The size of the vanguard cohort should be based on the expected incidence of side effects in the placebo group and the acceptable incidence in the treatment group. This may require additional recruitment to the vanguard cohort prior to the start of to the phase III trial.
All phase III chemoprevention trials could potentially benefit from inclusion of a vanguard cohort. The more intensive monitoring of the vanguard cohort allows the larger efficacy cohort to have a more streamlined, cost-effective side effect evaluation and management protocol.
When Should Phase I/II Trials Be Completed?
Many naturally occurring as well as synthetic compounds have shown chemoprevention activity. These range from micro-
utrients to synthetic enzyme inhibitors. Some of these agents are thought to be free of side effects where others are clearly
toxic. The decision to conduct a phase I and II should be made on an agent-by-agent basis. Because these trials have a primary objective of side effect evaluation, this decision is driven by the concern for side effects.
Many micronutrients with potential chemoprevention activity are currently available as over-the-counter supplements. These include low doses of vitamin E, ascorbic acid, β-carotene, vitamin A, selenium, and others. Although placebo-controlled trials of low dose supplementation have not been done, their long time use by the general public implies relative safety. For these compounds (in low doses), it is unlikely that the short
ability are currently available as over the counter must be considered as a group of agents
able over the counter must be considered as a group of agents with a less clearly defined potential for side effects. For many
These include low doses of vitamin E, ascorbic acid, β-carotene, vitamin A, selenium, and others. Although placebo-controlled
tried in a phase II trial of these agents. A phase IIB trial of these agents (the investigation of intermediate end points) would be of value since this may provide new information.
In general, micronutrients in higher doses than those available over the counter must be considered as a group of agents

Phase III Trial
The objectives and design of phase III trials are beyond the scope of this article. However, in the context of a discussion of phase I and II trials, the phase III trial is the most effective forum to determine side effects of a chemoprevention agent. The potential for detecting differences in the incidence of side effects between a placebo and an active agent becomes possible when studying large populations over a prolonged period of time (the usual scenario for phase III trial). It is important to remember that any agent appropriate for a phase III trial is unlikely to have significant side effects during its phase I and II evaluation. Hence, side effect monitoring in phase III trials, should focus on detecting common and uncommon long term side effects.
The Vanguard Cohort: Long Term Side Effect Evaluation. Because of the difficulty in determining long term side effects of chemoprevention agents, our group has introduced the concept of the vanguard cohort. The evaluation of long term side effects will vary with the target population, the specific agent, and its expected duration of use. It is impractical to complete a 10+-year phase I or II trial to prove safety and then initiate a trial to determine efficacy. The concept of the vanguard cohort allows the evaluation of long term side effects simultaneously with the phase III trial.
Phase II trials of an agent are in general initiated 2–4 years prior to the start of a phase III efficacy evaluation. If it is decided to proceed with a phase III evaluation, the phase II cohort can then continue to be followed in parallel for the duration of the phase III evaluation. This phase II cohort is now considered as the vanguard cohort. The built-in 2–4-year advance exposure of this group to the intervention agents results in the vanguard cohort’s always have a longer exposure to the agents than the larger phase III cohort. Hence, long term side effects will vary with the target population, the specific agent.

Phase I and II Trials of Chemoprevention Agents

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and intermediate end point information is not available. For other agents such as \( \beta \)-carotene, retinol, 13-cis-retinoic acid, and etretinate which have been in clinical use for many years, a large body of information exits about their clinical toxicity and pharmacology. For these agents, formal phase I trials are unnecessary.

Another group of agents is that with a low incidence of acute toxicity but with poorly defined levels of chronic toxicity. Tamoxifen is an example of such an agent. It is widely used in the treatment of hormone receptor-positive breast cancer and has been suggested for use in breast cancer chemoprevention. While the incidence of acute side effects is low, the long term (10+ years) side effects are unknown. This and other agents with low potential for acute toxicity will need a thorough evaluation of chronic side effects. Phase I trials are unnecessary since previously undescribed side effects are unlikely in a small population studied for 6 months–1 year. Phase II trials are also unlikely to add new side effect information. These agents will require a long term trial in a large population to assess their potential for side effects. This usually occurs in the context of a phase III trial.

New agents or agents with little clinical investigation are analogous to a new cytotoxic agent and should have both a phase I and II evaluation.

Hence, the decision to complete a phase I or II trial will need to be on an agent-by-agent basis. Some agents may have a large amount of information available on acute side effects but little available on long term side effects. For others, the opposite may be true. The unique aspects of the clinical application of chemoprevention agents must be considered when determining the route of development of an agent.

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References

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