



Eugenio Eduardo Zampighi, 1859-1944. *The Peasant Family*. Oil on canvas, 21¾" × 30¼".
Courtesy of the Callan Fine Art gallery, New Orleans, Louisiana.

Several hurdles need to be overcome before large clinical chemoprevention trials for melanoma can be launched.

Chemoprevention of Melanoma: Theoretical and Practical Considerations

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Background: Chemoprevention refers to the use of agents to reverse, suppress, or prevent carcinogenic progression of cancer. The use of chemoprevention is an unexplored strategy in melanoma prevention.

Methods: A retrospective review of the literature was undertaken regarding the important elements in evaluating chemoprevention as a strategy in melanoma.

Results: Several considerations need to be addressed before a chemoprevention agent can be moved to a large randomized trial. Statins have both experimental and epidemiologic evidence to support their further development as candidate chemopreventive agents, but the evidence is insufficient to justify large-scale phase III studies. A strong scientific rationale, a systematic approach to chemoprevention agent development with rigorous chemoprevention designs, and careful selection of surrogate endpoint biomarkers are critical issues in developing a chemoprevention strategy.

Conclusions: Addressing these relevant considerations will allow for the development of chemoprevention in melanoma.

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Introduction

Chemoprevention of melanoma has been suggested as an unexplored strategy in melanoma.¹ Chemoprevention refers to the use of agents to treat cancer by reversing, suppressing, or preventing its carcinogenic progression.² The prerequisites for this approach in melanoma have been reviewed,^{1,3} and statins, the lipid-lowering drugs, have been suggested as promising chemoprevention agents.⁴

The completion of large clinical cancer chemoprevention trials has raised awareness of the importance and potential of this approach to cancer control.⁵ However, to date, results have been mixed. In breast cancer, tamoxifen

has been a successful chemoprevention agent, fulfilling the three levels of chemoprevention, although the risks of endometrial cancer have tempered the enthusiasm and opened the door for newer agents. In other settings, large randomized trials based on epidemiologic observations have yielded disappointing results in cervical cancer⁶ and colorectal cancers,⁷ as well as adverse results from beta carotene supplementation in smokers.⁸ The considerations that have resulted from these negative trials are relevant to all cancer chemoprevention strategies.⁹ Attention to these issues is needed before chemoprevention of melanoma can become a reality. In particular, a strong scientific rationale, a systematic approach to chemoprevention agent development⁹ with rigorous chemoprevention designs,¹⁰ and careful selection of surrogate endpoint biomarkers are critical.

Strong Scientific Rationale

In cutaneous melanoma, cancer is a consequence of detrimental gene-environment interactions, with the environmental agent widely accepted as ultraviolet (UV) radiation.¹¹ Similar to other cancers, UV-induced melanoma is recognized as a multistep process.⁴ Recent data suggest that alterations of ras pathway genes are critically important in the pathogenesis of sporadic melanoma. Several groups have demonstrated that *N*-ras and B-RAF mutations rarely overlap.¹²⁻¹⁵ It is therefore believed that *N*-ras and B-RAF mutations represent alternative genetic changes that result in the activation of the same signaling pathway, the Ras/ERK/MAPK cascade, driving tumorigenesis. The precise contribution of this pathway to melanoma is not known; however, combinations of B-RAF and p16 events are likely relevant. To date, the clinical data on sorafenib (BAY 43-9006, a C-Raf/B-Raf inhibitor) currently under investigation in metastatic melanoma patients provide a proof of concept on the relevance of targeting ras pathway signaling in melanoma.³ Currently, three candidate chemoprevention agents fulfill this scientific rationale: (1) apomine, a bisphosphonate ether, (2) perillyl alcohol, a monoterpene isolated from essential oils, and (3) statins.⁴ Several lines of evidence indicate that these agents target ras pathway signaling.⁴ Among these three agents, statins have been the focus of much attention as potential chemopreventive agents.^{4,16,17}

Development of Chemoprevention Agents

Results from clinical chemoprevention trials indicate that epidemiologic observations alone are insufficient to prompt the development and conduct of a phase III trial. Meyskens and Szabo⁹ suggested several levels of evidence that should be evaluated prior to moving a potential chemopreventive agent to large randomized trials (Table).

In the ideal scenario, agents that are selected for development should have evidence of potential activity based on data from experimental (mechanistic, in vitro, animal), epidemiologic (case-control, cohort, ecologic, secondary analyses), and clinical (phase I, IIA, IIB) trials. With statins, experimental and epidemiologic evidence supports them as chemopreventive agents in melanoma. In particular, considerable mechanistic, in vitro, and animal (experimental) data is available on the use of statins.³

With regard to epidemiologic evidence, in the largest observational (case-control) study evaluating statin use and cancer incidence,¹⁸ statin users had a lowered incidence of cancer vs nonusers (3,129 vs 16,976, respectively; odds ratio [OR] = 0.80; 95% confidence interval [CI], 0.66-0.96). The OR of cancer risk for those using statins for over 4 years was 0.64 (95% CI, 0.44-0.93). In melanoma, one secondary analysis of a cardiovascular trial has suggested a protective effect for those taking statins.¹⁹ Unfortunately, the cumulative secondary analysis data on melanoma incidence in cardiovascular trials employing statins for more than 4 years have to date indicated no significant protective effect of long-term statin therapy on risk of melanoma (Dellavalle R, personal communication, Melanoma Prevention Working Group, Tampa, Florida, November 20, 2004). Thus, while there is some epidemiologic evidence for the use of statins in melanoma, additional epidemiologic and clinical data will be necessary for these agents to fulfill the criteria proposed by Meyskens and Szabo⁹ and hence to justify the cost and effort of a phase III prevention trial.

Criteria of Evidence to Move Chemopreventive Agents to Large Randomized Trials*

Experimental evidence		Low
Mechanism	Low	↓
In vitro	↓	
Animal	High	
Epidemiologic evidence		
Case control	Low	
Cohort/ecologic	↓	
Secondary analysis	High	
Clinical evidence		
Biomarker	Low	
Preneoplasia	↓	
Neoplasia	High	
Trials		
Phase Ia/Ib	Low	↓
Phase IIa biomarker/dose-response	↓	
Phase IIb biomarker/dose-response	High	
Other beneficial effects on health (eg, prevention of CAD, osteoporosis)		+++

* The authors have also proposed a point system to ensure that evidence from multiple weak studies would not have more weight than the evidence from one stronger study. From Meyskens FL, Szabo E. How should we move the field of chemopreventive agent development forward in a productive manner? *Recent Results Cancer Res*. 2005; 166:113-124. Reprinted with kind permission of Springer Science and Business Media.

Intermediate Markers

The greatest challenge to developing a chemoprevention approach in melanoma will be to identify and validate intermediate markers that not only have predictive value, meaning they can be modulated by the agent of interest, but also — and more importantly — have prognostic value to indicate the likelihood of developing melanoma.²⁰ The caveat is that even if the chosen marker has good prognostic ability and can be modulated by the chemopreventive agent, it is important to note that modulation does not necessarily equate with a change in the incidence of the true endpoint, cancer incidence.⁹

Determining the best type of intermediate marker — clinical, histologic, biochemical, molecular, or genetic — may be another issue. Genetically engineered mice have helped identify a number of important molecular pathways in melanoma,⁴ and taking advantage of these models to determine the best intermediate markers should be a priority.⁹ Tumor angiogenesis may have a particularly critical role in the early development of cancer, and hence inhibiting angiogenesis may ultimately prove to be important in cancer prevention. In melanoma, ras pathway signaling appears to be involved in tumor angiogenesis,²¹ so identifying angiogenic markers in melanoma that can be modulated therapeutically may be a successful approach. The recently described melanoma markers — vascular endothelial growth factor receptor-2 (VEGFR-2), which is associated with melanoma development and progression, and phospho-Akt, expressed with melanoma invasiveness²²⁻²⁴ — may be of particular interest.

Safety of Candidate Agents

A critical element in the identification of candidate agents is their short- and long-term toxicity. Drugs with low toxicity, both acutely and after long-term chronic administration, are necessary since chemopreventive agents are frequently given for 5 years or more and are taken by individuals who do not have cancer at the time of administration. Thus, tolerance for toxicity is low in the target subject population, and drugs with low toxicity have a greater chance of being moved forward along the clinical trials pathway. On the other hand, the drug dosages and durations explored in cancer prevention may be different than those used for other indications. Thus, an agent that appears to be safe for one indication may not be considered sufficiently safe for use as a cancer chemopreventive. Caution is always necessary, as illustrated by the growing concerns about COX-2 inhibitors and cardiac risk.²⁵ While the acute and chronic toxicities of statins are well known (liver enzymes elevation, myopathy, rhabdomyolysis), close monitoring in a clinical trial would still be indicated. Toxicity — particularly long-term toxicity, but also the subtle minor toxicities that can affect drug compliance

over time — can be underestimated in typical phase II studies. For this reason, Meyskens and Szabo⁹ recommend that placebo-controlled phase II trials be performed prior to definitive phase III randomized studies.

Among promising candidate chemoprevention agents to date, statins have the most elements of the first levels of evidence⁹ for movement towards clinical and human trials studies, even if the data do not currently support a phase III trial. Their efficacy in several other diseases commonly associated with aging, including established activity in vascular disease and promising results in neurodegenerative disorders,²⁶ is another advantage.⁹

Conclusions

Several considerations need to be addressed before a chemoprevention agent can be moved to a large randomized trial. Statins have both experimental and epidemiologic evidence to support their further development as candidate chemopreventive agents, but the evidence is insufficient to justify large-scale phase III studies. While statins appear to be promising agents, several others, not discussed (eg, green tea, curcumin, and vaccines^{4,27,28}) will likely be evaluated in the future. As yet, there are no data on valid intermediate markers for melanoma prevention, although the relevance of ras signaling and angiogenesis in melanoma allows for hypothesis generation and testing. Since rigorous chemoprevention design is critical, the Southwest Oncology Group (SWOG) has developed a phase IIB chemoprevention study of statins vs placebo in a population of patients with already-treated early-stage melanomas and the presence of clinically atypical nevi (as prognostic markers of increased risk for melanoma development and potential predictive markers of therapeutic effect). These nevi will be biopsied pre- and post-intervention and several markers will be evaluated, including those pertinent to the MAPK pathway. The study design will permit the prospective evaluation of biological markers in both blood and biopsied nevi. The principal hypothesis tested will determine whether statins can modulate angiogenic markers known to be present in atypical nevi. The randomized, placebo-controlled phase IIB trial will adhere strictly to rigorous chemoprevention design, taking into consideration the need for adequate power.⁶ Whether the hypothesis to be tested is valid remains to be seen. However, data generated from this trial and others like it will advance the study of melanoma chemoprevention and perhaps will ultimately lead to phase III trials that directly assess the impact on melanoma incidence in high-risk patients.

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