The Challenges of Chemoprevention: How Can We Develop Drugs to Treat Cancer Risk Instead of Metastases?

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Chemoprevention: How Can We Develop Drugs to Treat Cancer Risk Instead of Metastases?

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Moderator

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High Hurdles for Chemoprevention Drugs

• The target of chemoprevention is precancer, pathological or molecular, often asymptomatic
• Progression of precancer often requires decades; therefore, approvable endpoints for drugs might be delay of invasive disease rather than survival
• Efficacious drugs exist that target known genetic drivers of progression—therefore, safety, not efficacy is the issue
• Logical *non sequitur*—it’s hard to make asymptomatic people more well than they already are
• Since drug approvals require that benefit exceeds risk, extensive data is needed to demonstrate a favorable risk/benefit ratio
• High hurdles are surmountable, large markets exist
Human Carcinogenesis is a Multi-Year Process

Dysplasia=Intraepithelial Neoplasia (IEN)

- Normal
- Initiated
- Mild
- Moderate
- Severe
- CIS
- Cancer

Colon
- ADENOMA: 5–20 yrs
- TOBACCO USE: 4–10 yrs
- DYSPLASTIC ORAL LEUKOPLAKIA: 5–15 yrs
- SEVERE DYSPLASIA: 6–8 yrs
- CIN III/CIS: 10–20 yrs

Head & Neck
- BARRETT’S: est. 9–13 yrs
- SEVERE DYSPLASIA: est. 3–4 yrs

Esophagus
- ATYPICAL HYPERPLASIA: 14–18 yrs
- DCIS: 6–10 yrs

Cervix
- PIN: >10 yrs
- DCIS: 6–10 yrs

Lung (Smokers)
- PIN: >10 yrs
- DCIS: 6–10 yrs

Skin (Non-Melanoma)
- ACTINIC KERATOSIS: 30–40 yrs
- TIS: <5 yrs

Breast
- PIN: >10 yrs
- DCIS: 6–10 yrs

Prostate
- PIN: >10 yrs
- DCIS: 6–10 yrs

Bladder
- PIN: >10 yrs
- DCIS: 6–10 yrs

Molecular Biomarkers of Carcinogenesis

Dysplasia = Intraepithelial Neoplasia (IEN)


**Prostate**
- AR, SRD5A2, CYP17, GSTP1 Polymorphisms
- Genetic Susceptibility to Infection

**Colon**
- ↓APC, ↑BCL-2, ↑c-MYC
- Hypomethylation
- ↑RAS, ↑COX-2

**Breast**
- E2 Metabolism, Cyt P450, ↑ER, ↑PR, ↓DNA Repair
- ↑DNA Adducts, Genomic Instability, ↓Thrombospondin
- ↓p53, ↑Cyclin D1, ↓BRCA1, 2, ↑IGF, ↑Aneuploidy

**Lung**
- ↓3p, ↓9p, ↓13q, ↓5p, ↓P16
- ↑53, ↑K-RAS, ↑c-myc, ↓22q, ↓18q, ↑β-Catenin

**Head & Neck**
- ↓3p, ↓9p, ↓p53, ↓FHIT, ↓p16, ↓p19
- ↑Cyclin D1, ↑EGFR, ↑COX-2
- ↓6p, ↓8p23, ↓4q26-q28

**Esophagus**
- ↓p16, ↓p53, ↓DNA Content
- ↑EGFR, ↑VEGF, ↑Cyclin D1, ↑APC, ↑TGFα, ↑VEGF, ↑Cadherin

**Liver**
- HBV, HCV, Carcinogen/DNA Adducts
- ↑TGF, ↑IGF-2, ↑TNF-2, IL6, Genomic Instability
- Telomerase, c-MYC, ↓p53, ↓Rb, ↑IGF2-R, ↓PTEN, ↑DLCI, ↓p73, ↓E-Cadherin, Cyclin D, Cyclin E, p16, p21, p27, Aberrant Methylation

**Normal**
- Initiated
- Mild
- Moderate
- Severe
- CIS
- Cancer
“Field Cancerization”

Multiclonal Focal Expansions

Epithelial Sheet
Why Intraepithelial Neoplasia (IEN)?

• Risk Marker
  — Finding Those at Risk: Cohort Selection, Personalized Medicine

• Near Obligate Precursor

• Disease Marker

• Thus, Best Candidates as Surrogate Endpoint Biomarkers (SEBs) for Cancer Incidence/Cancer-Related Survival

• Best Site for Biopsy to Obtain Molecular Data

• Once Drivers Are Known, Blind Biopsies Are Possible
Colorectal Carcinogenesis: Adenoma–Carcinoma Sequence

5-20 yrs  ACF  5-15 yrs  ADENOMA  5-15 yrs  CARCINOMA

Dysplasia

Normal  Mild  Moderate  Severe  Cancer

APC  bcl-2  c-myc  Hypomethylation

K-ras  COX-2

SMAD 2  SMAD 4  DCC  STAT

p53  p16  7q  p15  8p

Bub1  22q  tPA  MMP

VEGF  CD44  CEA

Cyclin D1  E-Cadherin

FDA GI Advisory Committee
Recommendations March 2002

• **Question:** In randomized, placebo-controlled clinical trials of chemopreventive agents used as an adjunct to colonoscopic screening or surveillance, what would represent a clinically meaningful benefit (effect) for

  - **Reduction of adenomas**
    - 30-35% reduction of polyp number or 15-20% increase in polyp free patients
  
  - **Increase in time interval between colonoscopies**
    - 50% increase in time interval between colonoscopies
  
  - **Reduction in complications associated with polypectomies**
    - Reduction of 25-50% in complications (e.g., bleeding, perforation). Background complication rate is 0.3-0.5% of polypectomies

• **Conclusion:** The AACR IEN Task Force recommendations (2/2002) for clinical efficacy were essentially adopted by the GI Committee and were consistent with designs of on-going trials
Requirements for Successful Development of Cancer Preventive Drugs

Find Those at Risk: Cohort Selection
• In line with tenets of personalized medicine (e.g., treatment based on presence of defined risk biomarkers)
• Expand definition of IEN beyond histological lesion (e.g., gene expression profile, molecular lesions)

Find Those at Risk Who Will Benefit From Treatment
• Have IEN (modulatable biomarker, on the causal pathway; therefore likely predictive of outcome, hence clinical benefit)

Address Criteria for Drug Approval: Demonstrate Net Clinical Benefit/Need
• Demonstrate Disease is being treated
  —% Efficacy is adequate
  —% Benefiting from intervention is adequate
Address Criteria for Drug Approval: Demonstrate Net Clinical Benefit/Need (continued)

- Benefit is “better” than alternative interventions (i.e., other drugs, surgery, image-guided intervention)
- Treated incurring toxicity/mortality/QOL issues is less than for alternative interventions
- Risk of toxicity less than risks of not treating (i.e., toxicity/morbidity from treatment less than risk of cancer progression from no treatment)
  - Less invasive procedures
  - Less risk of toxicity from extended treatment
  - Less need for surveillance

Back-Up Slides
• **Issues:** Beyond the 3-year efficacy endpoint of decrease in adenomas or increase in adenoma free patients

• **Chronic safety**—How long? How many patients?

• **Rebound**—Need to prove that those ceasing active drug do not have a higher rate of new polyps than placebo control

• **Resistance**—Need to demonstrate that the effect of the drug does not diminish over time

• **Durability**—Need to demonstrate the duration of the effect of the drug once ceased

• **Answer:** Follow for 6 years, as this fits into standard of care colonoscopies at 3 years (efficacy endpoint) and 6 years. Original trial size sufficient for chronic safety evaluation, if additional data is acquired either in confirmatory trials or in post-marketing surveillance. Rebound, resistance, and durability can be addressed from years 3–6 in active drug arm, placebo or historical controls.
Treatment of DCIS

• Current treatment modalities for DCIS are surgery and radiotherapy, and they are extremely effective.

• Thus, the issue for personalized therapy is which and how many patients with DCIS can be treated more conservatively.

• Since DCIS is non-invasive, controversy exists about whether it should even be called carcinoma, thus providing an ethical opportunity in clinical trials to evaluate new modes of therapy.

• The new modes include:

  – Image-guided intervention and focal ablation with a variety of cytodestructive modalities (e.g., high frequency ultrasound);
  – Intervention with drugs to treat or prevent DCIS or ADH;
  – Active surveillance (requires risk-stratification of the original lesion and reliable monitoring methodology)
AACR Task Force on the Prevention of IEN

Treatment and prevention of intraepithelial neoplasia: an important target for accelerated new agent development.


Progress in chemoprevention drug development: the promise of molecular biomarkers for prevention of intraepithelial neoplasia and cancer--a plan to move forward
Rate of Neoplastic Progression

Exposure Dose

Rate of DNA Lesions

Rate of Mitogenesis

Rate of Mutagenesis

Rate of Apoptosis

Rate of Variant Clone

Formation

Rate of Clonal Expansion

Rate of Clonal Evolution

Rate of Mitogenesis

Exposure Dose

The Special Case of Screening and Prevention

- Cognitive dissonance comes from the thesis of many that “it is difficult to make healthy people better than they already are”, so it’s all about risk/benefit of the screening and/or preventive intervention.
- But because of selection, lead time, and other biases inherent in experimental designs, definitive risk/benefit assessment can for the most part only be determined using randomized trials.
- These trials are often of necessity large and complicated by the fact that the efficacy of screening/early detection is inseparable from the efficacy/morbidity of the therapy that follows.
- So the data from the large screening studies are interesting and each target organ is unique/ different and raises difficult questions for further scientific study and also national policy:
  - Lung cancer: Mayo clinic study, PLCO and NLST
  - Prostate cancer: PLCO, ERSPC, Pivot Study
  - Breast cancer: Digital Mammography Netherlands, US (DMIST)
  - Colon cancer: National Polyp Study
50% reduction in number/diameter cf. baseline (significant cf. placebo control)

0–20% reduction in number/diameter cf. baseline (reduction significantly <treatment group)

9p = LOH on 9p21   3p = LOH on 3p21   17p = 17p13
11q = LOH on 11q13   13q = LOH on 13q21   14q = LOH on 14q31-32.1

Needed to determine efficacy in treatment group:
Genotype profile equivalent to or less progressed than placebo control

Based on data of Califano et al., Cancer Res. 56: 2488–2492, 1996
Limit of Subclonal Detection