ABSTRACT SUMMARY

The development, evaluation and approval of promising agents for bladder cancer prevention (chemoprevention) depends upon the rational integration of four key components: a) Agents (pharmaceuticals, biologics and nutrients); b) Biomarkers (intermediate endpoints that predict for clinical response and risk reduction; c) Cohorts (well defined high risk target populations d) Designs (efficient trial designs linked to the clinical phase of development). The promise of this overall strategy is the ability to conduct faster, smaller and more cost effective trials which incorporate validated surrogate endpoints rather than conventional clinical endpoints (cancer incidence, recurrence and survival). Current National Cancer Institute (NCI) phase III bladder cancer chemoprevention trials in progress are described. Since most patients with superficial (transitional cell) bladder cancer present with early disease (Ta, T1, Tis lesions) that frequently recurs and is easily accessible by serial cystoscopy and urine cytology, bladder cancer serves as a powerful clinical for conducting prevention trials of new agents for a tobacco related malignancy.

INTRODUCTION

Bladder cancer will be diagnosed in an estimated 53,200 people in the United states in 2000: 38,300 cases in men, and 14,900 cases in women (1). Thus, bladder cancer will be the fourth most prevalent noncutaneous malignancy in men and the eighth most common cancer among women in the United States (U.S.). Almost all cases will be transitional cell carcinomas (TCCs). Approximately two-thirds of all diagnosed cases represented superficial bladder cancer (Ta, T1, Tis). World wide bladder cancer numbers are much greater: approximately 200,000 to 250,000 new cases are diagnosed annually, with a male to female ratio 3:1, and there are approximately
120,000 deaths annually (2). The estimated prevalence in the U.S. is over 600,000 cases (SEER Cancer Statistics Review, 1999). The incidence of bladder cancer increases with age: the mean age at diagnosis is 65 to 70 years, peaking in individuals older than 80. Of those initially diagnosed with superficial cancer confined to the mucosa and submucosa, recurrences occur in up to 85% (3). Since patients with superficial bladder cancer require long-term surveillance by repeat cystoscopies, it has the highest average cost of care per patient from diagnosis to death.

Epidemiologic studies have consistently found an association between exposure to tobacco and industrial carcinogens, e.g., aromatic amines, and the development of bladder cancer. Occupational exposure to various arylamines is associated with up to a 100 fold increased risk of bladder cancer. It is generally accepted that 50% of bladder cancers in men are associated with cigarette smoking. Several host factors have been implicated in susceptibility to bladder cancer. These include the ability to detoxify carcinogens, such as differences in individual patient acetylator phenotypes (e.g., NAT2 slow acetylators are at increased risk), GST phenotypes (e.g., GSTM1 homozygous deletion), defects in the P450 cytochrome system (CYP1A1), and differences in DNA repair enzymes (hMSH2) (4, 5). Susceptibility modifiers include use of non-steroidal anti-inflammatory drugs (NSAIDs) and vitamins (e.g., vitamins A and E, beta carotene) (6), consumption of fruits and vegetables (7), and fluid intake (8). It is believed that tobacco smoking results in the concentration of carcinogens in the urine, including 4 amino-biphenyl (4ABP), which causes pan-urothelial transformation (field cancerization), thereby causing a high rate of new and recurrent carcinoma throughout the urothelium (i.e., renal pelvis, bladder, prostatic urethra). There is increasing evidence to support the concept of histopathologic and biochemical changes associated with this field effect years in advance of overt malignancy. While primary prevention is ideal, the premalignant field serves as a useful target for prevention approaches.

Prevention can be conducted through both public health methods and medical treatments. Until recently, however, effective agents for cancer prevention were not available. Consequently, public health initiatives such as the promotion of healthy lifestyles, smoking cessation and increased consumption of fruits and vegetables have been the mainstay of prevention efforts. This changed with the successful introduction of intravesical BCG therapy for superficial bladder cancer (FDA approved in 1990 for carcinoma in situ); BCG represented the first approved “chemopreventive” for cancer. In addition, recent evidence suggests that “megadoses” of vitamins A, B6, C and E may decrease superficial bladder tumor recurrence in patients receiving BCG. These findings have helped guide efforts aimed at developing and testing defined natural substances and synthetic agents that have the potential to either prevent cancer initiation, or to block progression of premalignant lesions to invasive cancer.