CANCER CHEMOPREVENTION

Cancer Treatment and Research

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Preface

Great advances were made in the pharmacologic-based treatment of cancer in prior decades. However, despite a marked increase in our understanding of cell and molecular mechanisms underlying the neoplastic process, therapy for advanced disease remains limited. While the reasons for this are many, it is generally accepted that advanced neoplasms contain a relatively large number of genetic and molecular alterations contributing to the maintenance of the neoplastic process. Such a situation precludes easy pharmacologic intervention. However, our ability to detect cancer at an earlier stage, coupled with our increased understanding of carcinogenesis, are propelling both basic and clinical scientists to pursue early intervention/chemopreventive approaches. This is based upon the notion that fewer molecular aberrations are present early on in the disease process. It also takes advantage of the fact that advances in both technology, and in the field of cancer biology, coupled with a heightened vigilance, have increased our ability to detect early disease more readily.

The chemopreventive approach is highly attractive for a number of reasons. First, treatment of pre-neoplastic, or early neoplastic, lesions would prevent the significant mobility and mortality associated with advanced neoplastic disorders. Secondly, it becomes practically and conceptually much easier to target disease processes which contain a smaller number of causative molecular targets. While highly attractive from a theoretical point of view, however, significant practical limitations exist with respect to developing new and effective chemopreventive agents. Most importantly, practical clinical endpoints remain elusive. The current "gold standard" for chemoprevention is to measure the non-occurrence of disease in a treatment group by comparing its incidence to that of a control group. This type of clinical trial design is labor intensive, very costly and time-consuming, and, for practical reasons, cannot be employed for the rapidly increasing number of chemopreventive agents being identified. These practical considerations have led to the notion that intermediate biomarkers can be used as indicators of clinical efficacy. This is a logical approach, wherein validated intermediate biomarkers would allow relatively small chemopreventive trials to be conducted in a relatively efficient manner, in a short amount of time. However, there is no universal approach to the identification of intermediate biomarkers, and their method of validation has still not been proven.

The promise of chemoprevention of neoplastic disorders has recently been brought into the realm of reality with clinical trials such as the breast cancer prevention trial and tamoxifen. Thus, efforts are currently in the process of being re-focused based upon the valid supposition that a more effective approach to the treatment of cancer involves treatment early on in the disease process. This is a rapidly evolving field, whose goals are admirable. However, it is also a field in great flux whose practical goals have yet to be defined on many fronts. Under

such circumstances, it is always a productive endeavor to review the current state of the art of the field. A selected collection of knowledge can thus serve as a basis to focus further investigations. Thus, the focus of this book is to provide a relatively broad presentation of topics of particular relevance to the field of cancer chemoprevention. It is hoped that this book can serve as a reference source to aid the next steps in the process of developing useful and effective chemopreventive strategies for neoplastic disorders.

Raymond Bergan