Colorectal Cancer

Evidence-Based Chemotherapy Strategies

Edited by

Leonard B. Saltz, MD

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Preface

Management options for patients with colorectal cancer have undergone dramatic changes over the past decade. Whereas at the start of 1996 only one drug, 5-Fluorouracil, was available for the treatment of this disease, a mere 10 yr later, six drugs are licensed for use in colorectal cancer, and others are in the late phases of clinical development. Likewise, surgical and ablative options, as well as an array of supportive medications, have shown substantial progress and undergone a dramatic proliferation over the past decade.

With the increased number of therapeutic options from which to choose, the clinician is better able to offer effective therapy to the patient with colorectal cancer. The clinician is challenged, however, to keep up with the rapidly changing landscape and the rapidly emerging data that shape the options for treatment today and tomorrow. In this text, leaders in the management of colorectal cancer review the current literature that has led us to where we are today. Critical evaluations of the data are offered, and evidence-based recommendations are made.

The initial chapters update the current thinking on the biology of colorectal cancer, and methods of possible prevention, both from the points of view of chemoprevention and screening. The state of the art for use of both cytotoxic chemotherapy and the incorporation of the newer biological therapies are then reviewed. Practical chapters on radiological evaluation of colorectal cancer treatment, and nursing issues related to supporting the patient through chemotherapy are then presented. An additional chapter focuses on the specifics of pain management in colorectal cancer patients. Finally, a forward-looking chapter explores possible new paradigms under development for colorectal cancer treatment in the future.

The goal of *Colorectal Cancer: Evidence-Based Chemotherapy Strategies* is to offer the practitioner a concise, authoritative reference, so that the knowledge gained over recent years can be disseminated, digested, and rapidly applied to clinical practice. Clinicians who treat colorectal cancer are all too cognizant of the extensive work that remains to be done in terms of developing definitive treatments for this disease. While recognizing the long way that we have to go, I hope that *Colorectal Cancer: Evidence-Based Chemotherapy Strategies* will help practitioners appreciate the strengths, as well as the limitations, of the data that have recently emerged, thereby helping to allow all patients to benefit from the progress that has been made thus far.

Leonard B. Saltz, MD

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1 Molecular Biology of Colon Cancer

William M. Grady, MD

Summary

Colorectal cancer affects approx 140,000 people in the United States each year, resulting in more than 55,000 deaths. Colorectal cancer develops as the result of the progressive accumulation of genetic and epigenetic alterations that lead to the transformation of normal colonic epithelium to colon adenocarcinoma. The loss of genomic stability is a key molecular and pathophysiological step in this process and serves to create a permissive environment for the occurrence of alterations in tumor suppressor genes and oncogenes. Alterations in these genes, which include *APC, CTNNB1, KRAS2, BRAF, MADH4*/*SMAD4*, *TP53*, *PIK3CA*, and *TGFBR2*, appear to promote colon tumorigenesis by perturbing the function of signaling pathways, such as the transforming growth factor-β and PI3K signaling pathways, or by affecting genes that regulate genomic stability, such as the mutation mismatch repair genes.

Key Words: Colon cancer; mutation; oncogene; tumor suppressor gene; DNA methylation.

1. INTRODUCTION

Colorectal cancer (CRC) arises as the consequence of the progressive accumulation of genetic and epigenetic alterations that drive the evolution of normal colonic epithelial cells to colon adenocarcinoma cells. This process of colon carcinogenesis, which has been termed the polyp-carcinoma sequence, is believed to typically take place over 10–15 yr and involves concurrent histological and molecular changes. The subsequent effect of these genetic and epigenetic alterations on the cell and molecular biology of the cancer cells in which they occur is the acquisition of key biological characteristics that are central to the malignant phenotype. From the analysis of the molecular genetics of colon cancer, it has become clear that the formation of colon cancer involves a multistage process, which is currently characterized at the molecular level by the underlying form of genomic instability (i.e., the loss of the ability to maintain the wild-type DNA coding sequence and repair DNA mutations) present in the

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cancers. In this background of genomic instability, genetic and epigenetic alterations accumulate and cooperate with each other to drive the initiation and progression of colon cancer *(1–3)*.

Colon cancer appears to be most commonly initiated by alterations that affect the Wingless/Wnt signaling pathway. The initiated colon cancer then progresses as the result of the accumulation of sequential genetic or epigenetic events that either activate oncogenes or deactivate tumor suppressor genes that are involved in other signaling pathways, such as the RAS-RAF-MAPK pathway, transforming growth factor (TGF)-β pathway, and the phosphatidylinositol 3 kinase (PI3K)-AKT pathway *(4,5)*. Some of the alterations that have been convincingly shown to promote colon carcinogenesis affect *KRAS2*, *TP53*, the gene for p53, and elements of the TGF-β signaling pathway, such as *TGFBR2* and *MADH4*/*SMAD4*. The identification of these alterations has provided potential targets for the development of new therapies for the prevention and/or treatment of colon tumors (Fig. 1).

2. POLYP-CARCINOMA SEQUENCE

The evolution of normal epithelial cells to adenocarcinoma usually follows a predictable progression of histological changes and concurrent genetic and epigenetic changes. These gene mutations and epigenetic alterations provide a growth advantage to these mutant cells and lead to the clonal expansion of these altered cells. This process leads to the progression of adenomas to adenocarcinomas by the serial acquisition of genetic and epigenetic alterations that produce clonal heterogeneity followed by Darwinian evolution at the cellular level. Until recently, it was believed that only adenomatous polyps had the potential to undergo malignant transformation; however, it now also appears that a subset of hyperplastic polyps may have the potential to transform through a hyperplastic polyp-serrated adenoma-adenocarcinoma progression sequence *(6)*. Colon cancers arising through a hyperplastic polyp-serrated adenoma-colon cancer pathway appear to have a unique molecular as well as histological pathway through which they arise.

3. GENOMIC INSTABILITY

Genomic instability, which is the loss of the ability of the cell to maintain the fidelity of the DNA, is a fundamental aspect of the tumorigenesis process. At least three forms of genomic instability have been identified in colon cancer: (1) microsatellite instability (MSI), (2) chromosome instability (CIN; i.e., aneusomy, gains and losses of chromosomal regions), and (3) chromosomal translocations *(7)*. The etiology of CIN has only been identified in a small subset of colon cancers; however, MSI is known to result from inactivating mutations or the aberrant methylation of genes in the DNA mutation mismatch repair (MMR) family, which repairs DNA base-pair mismatches that arise during DNA

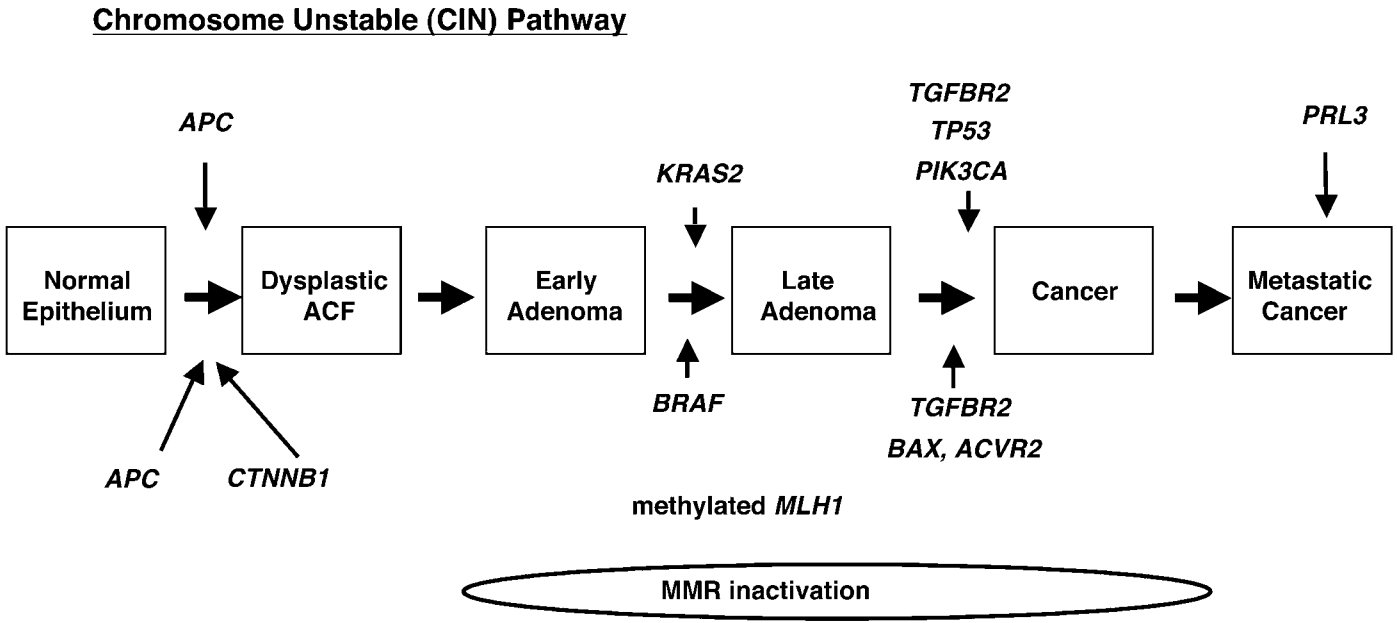

Fig. 1. Schematic representation of polyp-carcinoma progression sequence.

replication. Genomic instability contributes to the accumulation of mutations in tumor suppressor genes and oncogenes that drive the polyp-cancer progression sequence. The timing of the loss of genomic stability, either CIN or MSI, appears to be after adenoma formation but before progression to frank malignancy. In fact, both CIN and MSI can be detected in colon adenomas *(8–14)*. Shih et al. demonstrated that more than 90% of early adenomas (1–3 mm in size) exhibited allelic imbalance (also known as loss of heterozygosity [LOH]) of at least one of four chromosomes tested *(8)*. Ried et al. detected a stepwise increase in the average number of copy alterations using comparative genomic hybridization as adenomas progressed from low- to high-grade and then finally to carcinoma *(13)*. Despite the accumulation of data demonstrating the presence of genomic instability in early colon tumors, the causative role of genomic instability in cancer remains a source of considerable controversy *(2,7)*. Nonetheless, genomic instability is an attractive target for anticancer therapies because it is nearly ubiquitous in colon cancer and is a unique characteristic of cancer cells that is not present in normal epithelial cells. The feasibility of targeting genomic instability for anticancer treatments has been shown in in vitro systems *(15)*.

3.1. DNA Mismatch Repair Pathway/Inactivation of MMR Genes

Genomic instability arises because of inactivation of the normal mechanisms used by the cell to maintain its DNA fidelity. Defects in two of the systems that regulate DNA fidelity, the MMR system and Base Excision Repair (BER), have been identified in independent subsets of colon cancer. The DNA mismatch repair system (also known as the MMR system) consists of a complex of proteins that recognize and repair base-pair mismatches that occur during DNA replication. Inactivation of the MMR system occurs in 1–2% of CRCs owing to germline mutations in members of the MMR system, *MLH1, MSH2, PMS2*, and *MSH6*, and is the cause of the colon cancer family syndrome, hereditary nonpolyposis colon cancer (HNPCC) *(16,17)*. In addition to HNPCC-related colon cancers, approx 15% of sporadic colon cancers have inactivated MMR systems owing to the aberrant methylation of MLH1 (*see* p. 8) *(18)*. MSI occurs as the consequence of inactivation of the MMR system and is recognized by frameshift mutations in microsatellite repeats located throughout the genome. Because many colon cancers demonstrate frameshift mutations at a small percentage of microsatellite repeats, the designation of a colon adenocarcinoma as showing MSI depends on the detection of at least two unstable loci out of five from a panel of loci that were selected at a National Cancer Institute consensus conference *(19)*.

Study of the biochemistry of the MMR proteins has revealed that recognition of the base–base mismatches and insertion/deletion loops is performed by a heterodimer of either MSH2 and MSH6 or MSH2 and MSH3. Of interest, the MSH2–MSH3 heterodimer preferentially recognizes insertion/deletion loops and thus cannot compensate for loss of hMSH6. Consequently, cancers arising