EXPRESSION OF BCL-2 AND KI-67 IN COLORECTAL CARCINOMA

Immunohistochemical and Histopathological Study

Thesis

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ABSTRACT

Background: It is widely recognized that colorectal tumors of the same pathologic stage can produce considerably different clinical outcomes. Further identification of other factors that influence aggressiveness of the tumor are recommended. Cell proliferation and cell loss both determine the rate of volume increase of a tumor. Bcl-2 is an anti apoptotic marker and Ki-67 is a proliferation marker. **Aim of the Work:** This study aims at evaluation of expression of Bcl-2 and Ki-67 markers in colorectal carcinoma. **Material & Methods:** Evaluation of expression of Bcl-2 and Ki-67 markers in 60 cases of colorectal carcinoma was performed. **Results:** The commonest histologic type detected was adenocarcinoma **(80%)**, followed by signet-ring cell carcinoma **(10%)**, mucinous adenocarcinoma **(8.3%)**, and undifferentiated carcinoma **(1.7%)**, (P value <0.01). Histopathologic features including histological grade, local tumor extension, and lymph node involvement were found to have a statistically significant correlation with different colorectal carcinoma histopathologic types. 61.7% of the studied colorectal carcinoma cases were considered bcl-2 negative, and 38.3% were considered bcl-2 positive. Among positive cases 25% showed mild bcl-2 positivity, 11.7% showed moderate bcl-2 positivity, while only 1.7% displayed marked bcl-2 positivity with a statistically significant difference, (p value <0.01). The Ki-67 proliferation index values ranged from 0-100% with a mean of 65.57±32.829% and a median of 80%. **Conclusions & Recommendations:** Neither Bcl-2 nor Ki-67 is statistically related to age of patients, sex, clinical presentation, tumor site, gross appearance, histopathologic types, histological grade, local tumor extension, nodal involvement, and staging. Further investigations with a higher number of cases are needed to confirm the real significance of Bcl-2 and Ki-67 in colorectal cancer.

Key Words: Bcl-2, Ki-67, colorectal carcinoma.

LIST OF ABBREVIATION

ACI: Amsterdam Criteria I
ACII: Amsterdam criteria II
AJCC: American Joint Committee on Cancer
ANOVA: analysis of variance
APC: adenomatous polyposis coli
BAX: Bcl-2–associated X protein
Bcl-2: B-cell lymphoma-2
BMI: body mass index
BrdU: 5-bromodeoxyuridine
BrdUrd: bromodeoxyuridine
CDKs: cyclin-dependent kinases
CHRPE: congenital hypertrophy of the retinal pigment epithelium
C-myc: oncogene
CRC: colorectal carcinoma
CRM: circumferential resection margin
CTC: computed tomographic colonography
DAB: diaminobenzidine
DALM: dysplasia associated lesion or mass
DCBE: double-contrast barium enema
DCC: deleted in colon cancer
dH2O: distilled water
DNA: deoxy ribonucleic acid
FAP: familial adenomatous polyposis coli
FOBT: fecal occult blood test
FSIG: flexible sigmoidoscopy
G1 phase: gap 1 phase
H202: hydrogen peroxide
HNPCC: hereditary non polyposis colorectal cancer
HPF: high-power fields
IARC: International Agency for Research on Cancer
ICG-HNPCC: International Collaborative Group on HNPCC
IGF2: Insulin-like growth factor 2
IUrd: iododeoxyuridine

JP: Juvenile polyposis
K-ras: oncogene
LI: labeling index
LOH: loss of heterozygosity,
mAb: momoclonal antibody
MAP kinase: Mitogen-activated protein kinase ,
MMP7: matrix metalloproteinase 7
MMR: Mismatch Repair
MSI: microsatellite instability
MSI-H: high-frequency MSI
MSI-L: low-frequency MSI
MSS: microsatellite stable
P value: probability factor
p16: tumor suppressor
P53: tumor suppressor gene
PBS: phosphate buffered saline
PCNA: proliferating cell nuclear antigen
PET: positron emission tomography
PPARs: peroxisome proliferator-activated receptors
S100A4: metastasis promoting gene
SMADs: tumor suppressor
SPF: S-phase fraction
SPSS: Statistical Product for Services Solutions
TA: transitamplifying
TGF-β: transforming growth factor beta
TGFβR-II: transforming growth factor beta receptor-II
TME: total mesorectal excision
Tpot: potential doubling time
Ts: duration of S-phase
UC: ulcerative colitis
UICC: Union International Contre Le Cancer)
WHO: World Health Organization

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INTRODUCTION

Colorectal cancer is the third most common cancer and the fourth most frequent cause of cancer deaths worldwide. The WHO estimates that 945,000 new cases occur each year and despite surgical progress, colon cancer is responsible for 490,000 deaths annually in the world **(Weitz *et al*., 2005)**. Colorectal cancer represents the fourth and third most commonly diagnosed type of cancer among men and women respectively **(Jemal *et al*., 2008)**.

Currently, the most useful and widespread method of obtaining a guide to the prognosis in each individual case is through histopathologic confirmation of the adequacy of excision and the tumor stage as assessed by invasion of the tumor through the intestinal wall and determination of lymph node metastasis. This process is the basis for all of the major staging methods used for this particular type of cancer and has been proven to provide the best indication of prognosis. However, it is widely recognized that tumors of the same pathologic stage can produce considerably different clinical outcomes, thereby highlighting the necessity for further identification of other factors that influence prognosis independent of tumor stage (i.e., independent prognostic markers) **(Lyall *et al*., 2006)**.

The rate of cancer growth depends on proliferative activity and tumor cell death rate **(Ustymowicz *et al*., 2009)**. For a long time, dysregulation of cell growth leading to cancer was explained largely in terms of increased cell proliferation. It has become clear now that decreased cell death (apoptosis) may also contribute to the pathologic cell accumulation in a neoplasm. Enhanced cell survival through inhibition of apoptosis may be one of the mechanisms through which tumor promoters exert their effect **(Scopa *et al*., 2003)**.

Bcl-2 oncoprotein inhibits apoptosis both physiologically and pathologically. So the overexpression of Bcl-2 contributes to neoplasic transformation. It was initially found in B-cell follicular lymphomas. Abnormal activation of the Bcl-2 gene is both frequent and early in colon carcinogenesis.