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CORRELATION OF BIOLOGICAL MARKERS IN COLORECTAL CANCER TO CLINICAL OUTCOME OF THE DISEASE

Thesis
Submitted for partial fulfillment of
MD degree of medical oncology

BY

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Abstract

This prospective study included patients with pathologically proved metastatic colorectal cancer, who presented to the Medical Oncology Department of the National Cancer Institute in Cairo in the period between January 2002, and January 2004. The median age was 47 years and treated with the de Gramont regimen that utilizes both "prolonged infusion" and biomodulation; It comprises a 2-hour intravenous infusion of FA (200 mg/m2) followed by intravenous bolus 5-FU (400 mg/m2) and a 22-hour intravenous infusion of 5-FU (at a dose of 600 mg/m2). This is repeated on day 2, and the whole cycle is repeated every 14 days. The objectives were to determine the expression levels of three metabolic enzymes of fluoropyrimidines: thymidylate synthase (TS), thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD) and detect the presence of the microsatellite instability (D2S177) and correlate all these molecular markers with other prognostic factors, response and survival. There is significant correlation between low DPD expression and response to 5-FU (P= 0.003), in contrast to TS level, there is strong correlation between high TS expression and response (P=0.007). In case of the correlation of DPD expression and the toxicity; there was (67.9%) grade III-IV toxicity in the deficient group in contrast to (37.5%) in the low expression group (P= 0.06). No significant correlation could be detected in TP and MSI (D2S177) with the other prognostic markers.

Key words: Colorectal cancer, Thymidine synthase, Thymidine phosphorylase, Dihydropyrimidine Dehydrogenase, Microsatellite instability, Prognosis

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Gehan Rizk

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5'DFCR	5' deoxy -5 Fluorocytidine
5-FU	5 – fluorouracil
5-FUdR	5'- fluoro 2' –deoxyuridine
5-FUH_2	Dihydrofluorouracil
5-FUR	5- fluorouridine
5-FUTP	5-fluorouridine triphosphate
AFAP	Attenuated familial adenomatous polyposis
AIO	Arbeitsgemeinschaft Internische Onkologie
AJCC	American Joint Committee on cancer
ANC	Absolute neutrophilic count
APC	Adenomatous polyposis coli
ASI	Active specific immunity
ASO	Allele specific olignoucleotide analysis
ATP	Adenosine triphosphate
B – cat	Beta catenin
BAX	Bcl2- associated X Protein
BCG	Bacillus Calmette Guariane
BCL_2	B- cell leukemia/lymphoma 2
BMPR1A	Bone morphogenic protein receptor 1-A
BSA	Bovine serum albumin
CD	Cluster of differentiation
CDC 2- kinase	Cyclin dependent
CDDP	Cis dichloradiammineplatinum
c-DNA	core- Deoxyribonucleic acid
CEA	Carcinoembryonic antigen
CHEK2	Gheck point
CI	Continuous infusion
CI	Confidence interval
CIN	Chromosomal instability
C-MYC	Myelocytomatosis oncogen
COX	Cyclo-oxygenase
CPS	Cancer Prevention Study
CPT 11	Irinotecan
CR	Complete response
CRC	Colorectal cancer
CRM	Circumferential resection margin
CRM	Circumferential margin
CSA	Cryosurgery
C-SRC	Cellular Sarcoma
CT	Computed tomography
CTC	Common toxicity criteria
CTP	Cytidine triphosphate
DACH	Diaminocyctohexane
DCC	Deleted colorectal cancer
DLTs	Disease Limited toxicity
DNA	Deoxyribonucleic acid

DPD	Dihydropyrimidine dehydrogenase
DSH	Disheveled (DSH) signaling protein
dTDP	Thymidine diphosphate
dTMP	Thymidylate
dTTP	Thymidine triphosphate
dUMP	Deoxyuridylate
E – cad	E- cadherin
ECOG	Eastern Co-operative Oncology Group
EGFR	Epidermal growth factor receptor
ELISA	Enzyme linked immunosorbent assay
EU	Eniluracil
EUS	Endorectal /Ultrasound
F	Female
FA	Folinic acid
FAP	Familial adenomatous polyposis
FDA	Food drug administration
FDG –PET	Fluorodeoxyglucose positron emission scan
FdUMP	5- Fluoro – 2 deoxyuridine monophosphate
FOIFIRI	Irinotecan + 5-FU+ Folinic acid
FOLFOX	Oxaliplatin + 5-FU+ Leucovorin
FUDP	Fluorouridine diphosphate
FUMP	fluorouridine monophosphate
FUTP	Fluorouridine triphosphate
GA	Guanine adenine
G-CSF	Granulocyte colony stimulating factor
GI	Gastrointestinal
GITSG	Gastrointestinal study group
GSH Transferease	Glutathione S transferase
GSK3	Glycogen synthase kinase – 3
HAI	Hepatic Arterial Infusion
HBCC	Hereditary breast and colon cancer
hDig	Homologue of dorsophilla disc protein
Her-2 neu	C erb B2 (cellular erythroblastic leukemia oncogene)
hMLH1	Human mult homolog1
$hMSH_2$	Human must homolog 2
HNPCC	Hereditary non polyposis coli cancer
hPMS1 and hPMS2	Human postrmeiotic segregation 1 and 2
HR	Hazard Ratio
I.V	Intravenous
ICG	International Collborative Group
IFL	Irinotecan + 5-FU+ Leucovorin
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMC – C225	Cetuximab
IMPACT	International multicenter Pooled analysis of colon cancer trials
INT	Intergroup
IROX	Irinotecan + Oxaliplatin
KD	Kilo Dalton
K-RAS	Kirsten Rat Sarcoma oncogene

LD	Longest Diameter
LN	Lower normal
LOH	Loss of heterozygocity
LR	Local Recurrence
LV	Leucovorin
M	Male
M	Month
MCC	Mutated colorectal cancer
MMP-7	Matrix metalloprotease – 7
MMR	Mismatch repair
MOF	Mustine, Oncovine, Fluorouracil
MRI	Magnetic resonance imaging
mRNA	Messenger - RNA
MSI	Microsatelite instability
MSS	Microsatellite stable
MT	Microtubules
MTX	Methotrexate
MVC	Microvessel count
MVD	Microvessel Density
NACCP	Netherlands adjuvant colorectal cancer project
NCCTG	North Central Cancer Treatment Group
NCI	National Cancer Institute
NIH	National Institute of Health
N-Ras	Neuroblastoma Rat Sarcoma oncogene
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSAIDS	Non steroidal anti inflammatory drugs
OR	Odds ratio
OS	Overall survival
Oxal	Oxalilatin
PALA	Phosonactyl L- ascorpic acid
PARP	Plasminogen activation related parameters
PBS	Phosphate Buffer Saline
PCNA	Proliferating cell nuclear antigen
PCR	Polymerase chain reaction
PD	Progressive disease
PETACC	Pan European trial in adjuvant colon cancer
PJS	Peutz jeghers syndrome
PR	Partial response
PS	Performance status
QoL	Quality of life
RASCAL	Rapid Scanning and Correlation of Multiple Sequence Alignments
RFA	Radiofrequency ablation
RNA	Ribonucleic acid
RR	Response rate
RR	Relative risk
RT	Reverse trascriptase
RT-PCR	Reverse transcriptase- polymerase chain reaction
SD	Stable disease