Low Dose Capecitabine as Maintenance Therapy in Colorectal Cancer with Irresectable Metastasis

Thesis

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List of abbreviations

5-FU:	5 flurouracil
AAPC:	attenuated adenomatous polyposis coli
ACF:	aberrant crypt foci
ADL:	average daily living
AFAP:	attenuated familial adenomatous polyposis
AJCC:	American Joint Committee on Cancer
APC:	adenomatous polyposis coli
BEV:	bevacizumab
bFGF:	basic fibroblast growth factor
BSA:	body surface area
CAP:	College of American Pathologists
CEA:	carcinoembryonic antigen
CEPs:	circulating endothelial progenitor cells
CFI:	chemotherapy free interval
CI:	confidence interval
CIMP:	CpG island hypermethylation phenotype

CK1α: Casein kinase 1α

CRC: Colorectal cancer

CT scan: computed tomography scan

CT: chemotherapy

CTCAE: Common Terminology Criteria for Adverse Events

DCC gene: deleted in colorectal cancer gene

DCC: duration of disease control

DKK1: Dickkopf-1

DSH: disheveled (protein)

ECG: electrocardiogram

ECOG: Eastern Cooperative Oncology Group

ECs: microvascular endothelial cells

ECM: extracellular matrix

EGFR: Epidermal growth factor receptor

EMT: epithelial-mesenchymal transition

ERUS: Endorectal ultrasound

FAP: Familial adenomatous polyposis

FZD: Frizzled

GI: gastrointestinal

GSK3β: glycogen synthase kinase 3β

H: hours

HFS: hand-foot syndrome

HNPCC: Hereditary nonpolyposis colorectal cancer

HR: hazard ratio

HS: highly significant

IQR: interquartile range

IVF: intravenous fluids

LNs: lymph nodes

LOH: loss of heterozygosity

LV: lecuvorin

M: distant metastases

MAPK: mitogen activated protein kinase

mCRC: metastatic colorectal cancer

MCV: mean corpuscular volume

Mets: metastases

MMP: membrane-type 1

MMPs: matrix metalloproteinases

MMR: mismatch repair

MRI: magnetic resonance imaging

MSI: microsatellite instability

MSI-H: high-frequency microsatellite instability

MSI-L: low-frequency microsatellite instability

MSS: microsatellite stable

MT: microtubule

MTD: maximum tolerated dose

N: number

N: regional lymph node

NS: non-significant

ORR: overall response rate

OS: overall survival

PDGF: platelet-derived growth factor

PDGFRs: platelet-derived growth factor receptors

PET: positron emission tomography

PFS: progression free survival

PIP_3: phosphatidyl-inositol-3-phosphate

PlGF: placental growth factor

PPE: palmar-plantar erythrodysesthesia

PO: per os

PS: performance status

PTEN: phosphatase and tensin homolog

Pts: patients

QOL: quality of life

S: significant

SD: mean standard deviation

SD: stable disease

SEER: Surveillance, Epidemiology, and End Results

SFRP: secreted-frizzled-related-protein

Std: standard

T: tumor

TCF: T-cell factor family

TGF β: transforming growth factor β

TKI: tyrosine kinase inhibitor

TP: thymidine phosphorylase

TPN: total parentral nutrition

TSP-1: thrombospondin- 1

TTP: time to progression

UC: ulcerative colitis

UICC: Union Internationale Contre le Cancer

ULN: upper limit of normal

VDAs: vascular disrupting agents

VEGF: vascular endothelial growth factor

VEGFR: vascular endothelial growth factor receptor

WIF1: WNT inhibitory factor-1

WT: wild type

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Introduction

Colorectal cancer is the third most frequently diagnosed cancer in men and women in the United States, where an estimated number of 108,070 new cases of colon cancer and approximately 40,780 cases of rectal cancer would occur, and 49,960 people would die from colon and rectal cancer in year 2008 ***(Jemal et al, 2008).***

The NCI in Egypt estimated colorectal cancer to be the 5th common incident cancer in both males and females, accounted for 4.2% of incident cases in males and for 3.8% in females ***(Elattar, 2005).***

Impressive gains in response rates, progression-free survival, overall survival, and -sometimes- potential cure were achieved in the past decade in the field of metastatic colorectal cancer treatment as a result of evolution of new chemotherapeutic agents ***(Goldberg et al, 2007).***

Addition of agents like oxaliplatin ***(De Gramont et al, 2000)*** and irinotecan ***(Saltz et al, 2000)*** to the standard 5-FU/leucovorin has improved efficacy over 5-FU/leucovorin alone. Targeted therapies as bevacizumab, cetuximab and panitumumab introduction have shown to increase response rates, progression-free survival, and -in the case of bevacizumab- overall survival, particularly when used in combination with cytotoxic chemotherapy ***(Tabernero et al, 2007).*** Capecitabine has proved to be an acceptable alternative for 5-FU, adding more treatment options ***(Cassidy et al, 2008).***

However, the abundance of the treatment options, despite offering prolonged survival to patients if they have access to these options, it also comes with specific

challenges, the most important of which is that the most effective sequence of agents, the best combination regimens, and the optimum duration of therapy remain not well defined ***(Grothey, 2007).***

The desire for less toxic regimens, and decreasing the need for hospitalization, with keeping the advantage of prolonging overall survival have changed current treatment approaches to an individualized therapeutic strategy, examples include the stop-and-go approaches with maintenance therapy phases, chemotherapy-free intervals, and reduced dosing less toxic maintenance regimens ***(Wu et al, 2008).***

Maintenance therapy or sometimes referred to as "metronomic" dosing is the chronic administration of an agent at relatively low, nontoxic doses on a frequent schedule of administration with no prolonged drug-free breaks ***(Kerbel and Kamen, 2004)***.

Some metronomic regimens can have surprisingly potent antitumor effects compared with respective maximum tolerated dose regimens, despite being less toxic ***(Bertolini et al, 2003)***, in addition to their anti-angiogenic activities attained by targeting proliferating endothelial cells in tumor blood vessels ***(Ooyama et al, 2008).***

Several trials are being performed to evaluate the efficacy, safety, and quality of life through the use of maintenance therapy in advanced colorectal cancer. This includes irinotecan ***(Loupakis et al, 2006)***, chronically administered infusion 5-FU ***(Marshall et al, 2007)***, and oral fluoropyrimidine ***(Scalamogna et al, 2007)***.