Predictors of Response to Adjuvant Chemotherapy for Colorectal Cancer

Thesis submitted for the degree of

Doctor of Philosophy

University of Adelaide

Department of Surgery

Health Sciences

By

Michelle Liza Thomas

MBBS FRACS

August 2009

Dedication

I dedicate this work to my late father,

Ormond James Thomas

who would have been very proud

and to my mother,

Robyn Arlene Thomas

who is such an inspiration

Abstract

Background:

It is well recognized that not all patients with stage C colorectal cancer (CRC) derive a survival benefit from adjuvant chemotherapy. It would therefore be advantageous to identify factors that define a target group for treatment. It has been suggested that those most likely to benefit are women with proximal tumours. Recent work has suggested microsatellite instability (MSI) may be a useful marker however the limited studies performed are conflicting.

Aim:

To determine if gender, site, tumour histology or microsatellite (MSI) status predict survival benefit from 5FU-based adjuvant chemotherapy in stage C CRC.

Method:

Data was collated on stage C colorectal cancer cases that underwent curative resection over a 20-year period (inclusive of years prior to standard chemotherapy). Pathology was re-evaluated, DNA extracted from the formalin fixed paraffin specimen and MSI status established. Primary endpoint was cancer-related death. Kaplan-Meier curves were constructed for univariate analysis and differences analysed by log rank test. Multivariate analysis was performed using Cox proportional hazard model adjusting for age, gender, site, distinct pathological variables and MSI. A compounding effect between these factors and chemotherapy benefit was measured by interaction testing

Results:

811 unselected cases were included in the study. Thirty-seven percent received chemotherapy. Chemotherapy significant improved cancer-specific survival (HR of dying 0.66 (95% CI 0.52-0.83 p=0.0003). Female gender offered a survival advantage overall (HR 0.81 95% CI 0.68-0.97; p=0.02) however site did not influence outcome (HR 1.03). On interaction testing, gender, site and tumour histology did not significantly influence the survival effect of chemotherapy.

802 cases were included in the MSI analysis of which 77 exhibited MSI. MSI status did not influence prognosis (HR of cancer death 1.45, 95% CI 0.90-2.21; p= 0.13). However, in the non-chemotherapy cohort, MSI conferred a significantly less favourable outcome (HR 1.89, 95%CI 1.13-3.16; p= 0.02). Chemotherapy produced a survival benefit in both the MSI (HR 0.08 95% CI 0.02-0.27; p=<0.0001) and the microsatellite stable (MSS) cohort (HR 0.62, 95% CI 0.47-0.81; p=0.001). On interaction testing, neither compounded the benefit of chemotherapy, however of all the tested parameters, MSI came closest to significance (p=0.08).

Conclusion:

These results suggest that 5FU-based adjuvant chemotherapy for stage C colorectal cannot be targeted using gender, tumour site, histological characteristics or MSI.

Short Table of Contents

Table of Contents

List of Tables

List of Figures

List of Abbreviations

5FU	5-fluorouracil
ACPS	Australian clinicopathological stage
AJCC	American Joint Committee on Cancer
APC	Abnormal in polyposis coli
Ams	Amsterdam criteria
C	Colon
C/R	Colon/rectum
CA	Cancer specific survival
CIMP	CpG island methylator phenotype
CpG	Cytosine phosphate bonded to guanine
CRC	Colorectal cancer
DCC	Deleted in colorectal cancer
DNA	Deoxynucleic acid
FAP	Familial polyposis coli
FFPE	Formalin fixed paraffin embedded
GIT	Gastrointestinal
GITSG	Gastrointestinal Study Group
HNPCC	Hereditary non-polyposis colorectal cancer
HR	Hazard ratio
ICG	International Collaboration Group
IDL	Insertion/deletion loop
IDS	International documentation system
IGF	Insulin like growth factor
JPS	Juvenile polyposis coli
LN	Lymph node
LOH	Loss of heterozygosity
MGMT	O6-methylguanine methyltransferase
MMR	Mismatch repair
MNNG	N-methyl-N-nitro-N-nitrosoguanidine
MSI	Microsatellite instability
MSI-H	Microsatellite instability high
MSI-L	Microsatellite instability low

MSS	Microsatellite stable
MV	Multivariate
n	Number
N/S	Not stated or specified
NA	Not assessable
NCI	National Cancer Institute
NS	Not significant
O/C	Outcome
OR	Odds ratio
OS	Overall survival
PJS	Pertz Jegher Syndrome
R	Rectal
RR	Relative risk
Ref	Reference
RER	Replication error
SIG	Significant difference detected
TGF	Transforming growth factor
TILs	Tumour infiltrating lymphocytes
TME	Total mesorectal excision
TS	Thymidate synthetase
UICC	International Union Against Cancer
uk	Unknown
UV	Univariate

Declaration

I declare that this work contains no material that has been accepted for award of any other degree or diploma in any university or other tertiary institution to Michelle Thomas and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to provision of the Copyright Act 1968.

I also give permission for the digital version of my thesis to be made available on the web, via the University‟s digital research repository, the library catalogue, the Australian Digital Thesis Program (ADTP) and also through web search engines, unless permission has been granted by the university to restrict access for a period of time.

Michelle Thomas

Acknowledgements

I am extremely grateful to all those that helped me in the preparation of this thesis. I wish to thank the following people in particular.

Supervisors

My supervisors for their enormous support, time, vision and patience.

Mr James Moore for his considerable time commitment, clear thinking and thoroughness.

Mr Peter Hewett for his ideas, humour and encouragement.

Dr Barry Iacopetta for his ideas and inspiration.

Laboratory

Dr Andrew Ruszkiewicz for his commitment to the massive task of re-evaluating all the pathology and making it an enjoyable and educational process.

To his laboratory staff for their assistance in slide processing, in particular Kay and Connie.

Mr Graeme Bennett and Mr Stuart Phyllis for teaching me the molecular biology laboratory methods and assisting with the DNA processing.

Department of surgery

Mr Neville DeYoung for always being helpful and available for administration matters

Ms Jenny Myers for her very valuable assistance in many matters, particularly formatting

Prof. Glyn Jamieson for his ability to understand the core of any issue and raise pertinent questions that enriched the thesis

And all the departmental staff whose assistance was invaluable and who provided a pleasant and supportive environment in which to work.

Other organizations

State Cancer Registry staff for assistance in collating state data.

RAH Cancer Registry staff for making available the hospital database

Hospital medical record staff for finding the numerous casenotes required, many of which had to be retrieved from archives.

Financial Assistance

University of Adelaide for an academic scholarship

Tyco Australia for the CSSA Scholarship, the funds of which contributed to the thoroughness of this study by funding much of the laboratory work

Statistics

Ms Kristen Willson, Ms Emmae Ramsay and Ms Janine Jones for their assistance in the statistical analysis of data.

Editorial

Mr Phil Thomas for correcting my English and grammar.

Other

Mr Mark Killingback – for his interest and encouragement upon my winning the award given in his name.

And last but not least my lovely family Ben, Oliver and Matilda Angel for enduring the process.

Presentations

Association of Coloproctology of Great Britain and Ireland (ACPGBI) Annual Conference 2006

Is Microsatellite Instability a Useful Molecular Marker to Target Chemotherapy in Colorectal Cancer?

American Society of Colon and Rectum Surgeons (ASCRS) Annual Conference 2006

Is Microsatellite Instability a Useful Molecular Marker to Target Chemotherapy in Colorectal Cancer?

Annual Scientific Congress, Royal Australasian College of Surgeons 2005

Is Microsatellite Instability a Useful Molecular Marker to Target Chemotherapy in Colorectal Cancer?

Awarded the Mark Killingback prize

Annual Scientific Congress, Royal Australasian College of Surgeons 2005

Pathological Predictors of Outcome in Colorectal Cancer

Annual Scientific Congress 2004

The Influence of Gender and Site on the Response to Adjuvant Chemotherapy in Colorectal Cancer