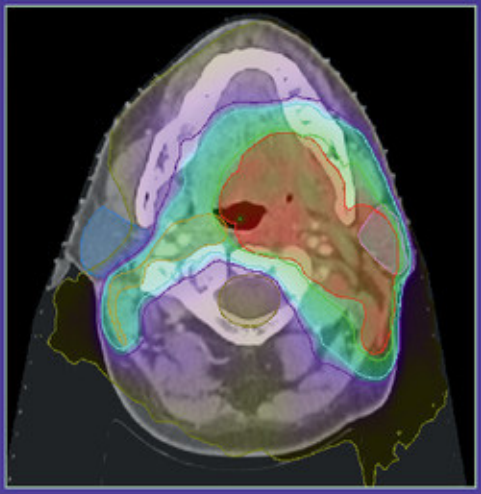

Practical Clinical Oncology

SECOND EDITION

Edited by Louise Hanna,
Tom Crosby and Fergus Macbeth

CAMBRIDGE Medicine

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Second Edition

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Preface to the first edition

This book is intended primarily for trainees in clinical oncology, but members of other professions such as medical oncology, surgery, palliative care, nursing and radiography will also find it useful. The book started life as a set of lecture notes from the Cardiff Annual FRCR Part II course, but has since grown to include more topics than could possibly be covered during the three days of that course. Our approach in producing this volume has been to focus on practical suggestions appropriate to day-to-day decision making during the treatment of oncology patients. We are very grateful to our colleagues from Velindre and elsewhere, who are listed on page xi, for reviewing specific chapters and ensuring that the advice contained within is as widely applicable as possible.

The first seven chapters cover 'generic' topics which provide background information on cancer treatments. These are chemotherapy, biological and hormonal treatments, radiotherapy planning, research, emergencies and palliative care. The chapters which follow each focus on a tumour site or tumour type. In this latter group, the chapter layout is fairly consistent to help the reader navigate through the book. Thus, each chapter begins with background information on tumour types, anatomy, incidence, epidemiology, risk factors and aetiology. Next there are sections on pathology, routes of spread and, where appropriate, screening. These are followed by clinical sections on presentation, investigations, treatment and prognosis. Most of the chapters also discuss areas of current interest and clinical trials, reflecting the rapidly changing nature of clinical oncology where many areas of practice are open to debate. Where references are given, we have tried as much as possible to include those key publications which have influenced clinical practice. Towards the end of the book there is a series of 'single best answer' multiple choice questions, which will give the reader the opportunity to test their knowledge.

In a book of this length, it is not possible to provide as much of the subject as would be found, for example, in the larger multivolume oncology textbooks. Nevertheless, an attempt has been made to give an overview of clinical oncology practice at the present time, which we hope will be of interest and benefit to trainees.

The idea for writing this book came about several years ago when two of the editors (TC and LH) were studying for their FRCR part II examination. They have since become consultants in Velindre Hospital with FM and all three now teach on the Cardiff Annual FRCR part II course.

Preface to the second edition

It is now seven years since the first edition of this book was published and during that time there have been major changes in the non-surgical management of patients with cancer with new systemic treatments and new radiation technology becoming more widely available. We have reflected these changes by thoroughly updating all the topics. The aim of the book remains the same – to provide all health professionals training in cancer-related specialties with succinct, up-to-date summaries of current practice.

As before, the book starts with introductory chapters covering generic topics such as chemotherapy, biological and hormone treatments, radiotherapy planning, research and palliative care. We have added new generic chapters on pathology and advanced external beam radiotherapy to reflect recent developments in these areas. The chapters on oncological emergencies and cancer of unknown primary have been placed together to recognise the developing concept of acute oncology. After the generic topics, the chapters each address the management of specific tumour types. The topics on the use of radiotherapy in benign diseases have been incorporated within these chapters. As with all textbooks of this type, there is a limit to the amount of detailed information that can be included and, in particular, topics in which there is rapid change or active research may become dated quite quickly. We have asked the authors to flag up important current clinical trials and potential new developments. There is a series of multiple choice questions at the end of the book. For readers who wish to test their knowledge, further multiple choice questions set at the level of the Final FRCR examination can be found in Oncopaedia (www.oncopaedia.com/ accessed February 2015).*

Although the book is still firmly rooted in the revision course run at Velindre Hospital in Cardiff for trainees taking the Final FRCR examination and reflecting contemporary clinical practice in the UK, we hope that it will still be informative for those from other specialties and from other countries. We hope you will enjoy reading and learning from this new edition.

** Please note that this website is recommended by the Editors but is not formally endorsed by Cambridge University Press.*

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Abbreviations

General

1D	1-dimensional
2D	2-dimensional
3D	3-dimensional
34βE12	mouse monoclonal antibody to high molecular weight cytokeratin
4D	4-dimensional
5AC	MUC subtypes A and C
5-ALA	5-aminolevulinic acid
5-FU	5-fluorouracil
5-HIAA	5-hydroxy-indoleacetic acid
5-HT3	5-hydroxy-tryptamine 3
5YS	five-year survival
αFP	alpha feto-protein
βhCG	beta human chorionic gonadotrophin
AAPM	American Association of Physicists in Medicine
ABC	activated B-cell-like; advanced bladder cancer
ABCSG	Austrian Breast and Colorectal Cancer Study Group
ABL	ABL proto-oncogene, non-receptor tyrosine kinase
ABPI	accelerated partial-breast irradiation
ACA	adenocarcinoma
ACE	anticholinesterase
ACh	acetylcholine
ACP	advanced care planning
ACTH	Adrenocorticotrophic hormone
ADC	apparent diffusion coefficient
ADH	antidiuretic hormone
ADI-PEG20	arginine deiminase formulated with polyethylene glycol
ADT	androgen deprivation therapy
AF	activating function
AFIP	American Forces Institute of Pathology
AFP	alpha feto-protein
AFX	atypical fibroxanthoma
AGES	age, grade, extent, size
AGITG	Australasian GastroIntestinal Tumour Group
AHT	adjuvant hormone therapy
AI	aromatase inhibitor
AIDS	aquired immune deficiency syndrome
AIN	anal intraepithelial neoplasia
AJCC	American Joint Committee on Cancer
AKT	thymoma viral proto-oncogene
ALK	anaplastic lymphoma kinase
ALL	acute lymphoblastic leukaemia
ALM	acral lentinginous melanoma
ALND	axillary lymph node dissection
AMES	age, metastases, extent, size
AML	acute myeloid leukaemia

AMP	adenosine monophosphate
ANC	absolute neutrophil count
ANO1	anoctamin 1, calcium-activated chloride channel
APBI	accelerated partial breast irradiation
A-P	anterior–posterior
AP-1	activator protein-1
ApC	antigen-presenting cell
APC	*adenomatosis polyposis coli*
AP/PA	anterior–posterior/posterior–anterior 'parallel-opposed'
APR	abdominoperineal resection
APUD	amine precursor uptake and decarboxylation
AR	androgen receptor
ARE	androgen response element
ARSAC	Administration of Radioactive Substances Advisory Committee
ASC	active symptom control
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ATAC	Arimidex, Tamoxifen, Alone or in Combination
ATD	amino-terminal domain
ATLAS	Adjuvant Tamoxifen: Longer Against Shorter
ATP	adenosine triphosphate
AUC	area under curve
AVM	arteriovenous malformation
B12	vitamin B12
BAP1	BRCA-associated protein
BC	British Columbia
BCC	basal cell carcinoma
BCG	bacillus Calmette–Guérin
BCIRG	Breast Cancer International Research Group
BCL	B-cell CLL/lymphoma
BCNU	bis-chloroethylnitrosurea; carmustine
BCR	breakpoint cluster region
BCS	breast-conserving surgery
BCSH	British Committee for Standards in Haematology
BCT	breast conservation therapy
b.d.	bis in die (twice a day)
BED	biologically effective dose
Ber-EP4	antibody against EpCAM; epithelial cell adhesion molecule
BEV	beam's eye view
BGND	bilateral groin node dissection
BIG	Breast International Group
BIR	British Institute of Radiology
BMD	bone mineral density
bNED	biochemical disease-free survival
BNLI	British National Lymphoma Investigation
BOADICA	Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
BP	blood pressure
bpm	beats per minute
BR	borderline resectable
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BRCA	breast cancer gene
BSA	body surface area
BSC	best supportive care
BSCC	British Society for Clinical Cytology
BSO	bilateral salpingo-oophorectomy
BTA	British Thyroid Association

BTK	Bruton's tyrosine kinase
BTOG	British Thoracic Oncology Group
BTS	British Thoracic Society
CA	cancer antigen
CAIX	carbonic anhydrase IX
CALGB	Cancer and Leukaemia Group B
CBCT	cone beam CT
CD	cluster of differentiation
CD117	KIT; v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog
CDCA1	cell division cycle associated 1
CDH1	cadherin 1
CDK	cyclin-dependent kinase
CDKN2A	cyclin-dependent kinase inhibitor 2A
CDX	caudal-type homeobox
CE	conversion electron
CEA	carcino-embryonic antigen
CG	Clinical Guideline
CgA	chromogranin A
CFS	colostomy-free survival
CHART	continuous hyperfractionated accelerated radiotherapy
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CIS	carcinoma *in situ*
CK	cytokeratin
C-Kit	KIT; v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog
CLA	common leukocyte antigen
CLIPi	Cutaneous Lymphoma International Prognostic Index
CLL	chronic lymphocytic leukaemia
CM	complete mole
c-Met	MET; MET proto-oncogene, receptor tyrosine kinase
CML	chronic myelocytic leukaemia
CNS	central nervous system; Clinical Nurse Specialist
COG	Children's Oncology Group of North America
COMS	Collaborative Melanoma Study
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CR	complete response
CRAF	C-Raf proto-oncogene, serine/threonine kinase: approved gene symbol = RAF1; approved gene name = Raf-1 proto-oncogene, serine/threonine kinase
CRH	corticotropin-releasing hormone
CRC	colorectal cancer
CRM	circumferential resection margin
CRMPC	castration-resistant metastatic prostate cancer
CRP	c-reactive protein
CRPC	castrate-refractory prostate cancer
CRT	chemoradiotherapy
CRT-S	chemoradiation followed by surgery
CRUK	Cancer Research UK
CSF	cerebrospinal fluid
CSS	cause-specific survival
cT	clinical tumour stage
ct	calcitonin
CT	computed tomography
CTAG	cancer/testis antigen
CTCAE	common toxicity criteria
CTCL	cutaneous T-cell lymphoma
Ct DT	calcitonin doubling time

CTLA4	cytotoxic T lymphocyte-associated protein 4
CTNNB1	catenin (cadherin-associated protein), beta 1, 88 kDa
CTV	clinical target volume
CTZ	chemoreceptor trigger zone
CUP	carcinoma of unknown primary
CVP	central venous pressure
CX	characteristic X-ray photon
CXR	chest X-ray
CYP	cytochrome P450
D2	dopamine D2
DAB	3,3-di-aminobenzidine tetra hydrochloride
DAHANCA	Danish Head and Neck Cancer
DCC	deleted in colon cancer
DCE	dynamic contrast enhancement
DCIS	ductal carcinoma *in situ*
dCRT	definitive chemoradiation
DDT	dichloro-diphenyl-trichloroethane
DES	diethylstilboestrol
DEPDC1	DEP domain containing 1
DFS	disease-free survival
DHA	dihydroxyandrostenedione
DHT	5α dihydrotestosterone
DLBCL	diffuse large B-cell lymphoma
DM	diabetes mellitus
d_{max}	depth of maximum dose
DMC	Data Monitoring Committee
DMSA	dimercapto succinic acid
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOG1	ANO1; anoctamin 1, calcium-activated chloride channel
DOPA	dihydroxyphenylalanine
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTANOC	DOTA-1-NaI-octreotide
DOTATATE	DOTA-octreotate
DOTATOC	DOTA-octreotide
DPC4	SMAD4; SMAD family member 4
DRE	digital rectal examination
DRR	digitally reconstructed radiograph
DSM	disease-specific mortality
DT	doubling time
DTC	differentiated thyroid cancer
DVH	dose–volume histogram
DW	diffusion-weighted
EBCTCG	Early Breast Cancer Trialists Collaborative Group
EBRT	external beam radiotherapy
EBUS	endobronchial ultrasound
EBV	Epstein–Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECS	extracapsular spread
EDTA	ethylenediaminetetraacetic acid
eGFR	estimated glomerulofiltration rate
EGFR	epidermal growth factor receptor
EIC	extensive intraductal component
ELND	elective lymph node dissection
EM	electron microscopy
EMA	epithelial membrane antigen
eMC	electronic Medicines Compendium
EMR	endoscopic mucosal resection
EMP	extramedullary plasmacytoma

ENETS	European Neuroendocrine Tumor Society
ENT	ear nose and throat
EORTC	European Organisation for Research and Treatment of Cancer
EPI	electronic portal imaging
EPIC	European Prospective Investigation into Cancer and Nutrition
EPID	electronic portal imaging device
EPO	erythropoietin
EPP	extrapleural pneumonectomy
EPSE	extrapyramidal side effects
EQD2	equivalent dose at 2 Gy
ER	oestrogen receptor
ERBB1	erb-b2 receptor tyrosine kinase 1: EGFR; epidermal growth factor receptor
ERBB2	erb-b2 receptor tyrosine kinase 2
ERBB3	erb-b2 receptor tyrosine kinase 3
ERBB4	erb-b2 receptor tyrosine kinase 4
ERCP	endoscopic retrograde cholangiopancreatogram
ERE	oestrogen response element
ERG	v-ets avian erythroblastosis virus E26 oncogene homolog
ESA	Employment and Support Allowance
ESMO	European Society for Medical Oncology
ESPAC	European Study Group for Pancreatic Cancer
ESR	erythocyte sedimentation rate
ESTRO	European Society for Therapeutic Radiology and Oncology
EU	European Union
EUA	examination under anaesthetic
EURAMOS	European and American Osteosarcoma Study Group
EUS	endoscopic ultrasound
EWS	EWSR1; Ewing sarcoma breakpoint region 1
FA	folinic acid
FAK	focal adhesion kinase
FAP	familial adenomatous polyposis
FBC	full blood count
Fc	constant region
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FEV-1	forced expiratory volume in 1 second
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FISH	fluorescent *in situ* hybridisation
FL	follicular lymphoma
FLI1	Friend leukaemia virus integration 1
FLIPI	Follicular Lymphoma International Prognostic Index
FLT3	fms-related tyrosine kinase 3
fms	peptide deformylase
FNA	fine-needle aspiration
FNAC	fine-needle aspiration cytology
FOB	faecal occult blood
FRCR	Fellow of the Royal College of Radiologists
FSH	follicle-stimulating hormone
FT4	free T4
FTC	follicular thyroid carcinoma
FU	follow-up
GBq	giga-Becquerel

GCB	germinal centre B cell-like
G-CSF	granulocyte colony-stimulating factor
GCP	good clinical practice
GCS	Glasgow coma score
GCT	germ cell tumour
GD2	ganglioside G2
GEC-ESTRO	Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GFR	glomerular filtration rate
GHSG	German Hodgkin Study Group
GI	gastrointestinal
GINET	GI-related neuroendocrine tumours
GIST	gastrointestinal stromal tumour
GLI	GLI family zinc finger 1
GM-CSF	granulocyte–macrophage colony-stimulating factor
GnRH	gonadotrophin-releasing hormone
GO	gastro-oesophageal
GOG	Gynaecologic Oncology Group
GOJ	gastro-oesophageal junction
GORD	gastro-oesophageal reflux disease
GP	general practitioner
GPA	granulomatosis with polyangiitis (Wegener's granulomatosis)
GSTM1	glutathione *S*-transferase mu 1
GTT	gestational trophoblast tumour
GTV	gross tumour volume
GU	genitourinary
Gy	Gray
GYN	gynaecological
H2	histamine H2
H_2O_2	hydrogen peroxide
HAART	highly active anti-retroviral therapy
HAL	hexyl ester hexaminolevulinate
HBF	heterotopic bone formation
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HDC	high dose chemotherapy
HDC/ASCT	high dose chemotherapy with autologous stem cell transplant
HDCT	high dose chemotherapy
HDR	high dose rate
HDU	high dependency unit
H+E	haematoxylin and eosin
HER	human epidermal growth factor receptor
HER1	human epidermal growth factor receptor 1: EGFR; epidermal growth factor receptor
HER2	human epidermal growth factor receptor 2: ERBB2; erb-b2 receptor tyrosine kinase 2
HER3	human epidermal growth factor receptor 3: ERBB3; erb-b2 receptor tyrosine kinase 3
HER4	human epidermal growth factor receptor 4: ERBB4; erb-b2 receptor tyrosine kinase 4
HES	hospital episode statistics
HGF	hepatocyte growth factor
HGFR	hepatocyte growth factor receptor
HGG	high grade glioma
HH	hedgehog
HHV	human herpesvirus

HIFU	high intensity focussed ultrasound
HIR	high intermediate risk
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HMB	human melanoma black
HNPCC	hereditary non-polyposis colorectal cancer
HNSCC	head and neck squamous cell carcinoma
hpf	high-powered field
HPOA	hypertrophic pulmonary osteo-arthropathy
HPV	human papilloma virus
HR	hazard ratio
HR-CTV	high-risk CTV
HRT	hormone replacement therapy
HSP	heat shock protein
HT	hormone therapy
HTP	hydroxytryptophan
hTERT	human telomerase reverse transcriptase
HTLV-1	human T-cell lymphotropic virus-1
IASLC	International Association for the Study of Lung Cancer
IBCSG	International Breast Cancer Study Group
IBIS	International Breast Cancer Intervention Study
ICAM1	intercellular adhesion molecule 1
ICC	interstitial cells of Cajal
ICD-10	International Statistical Classification of Diseases 10th revision
ICD-O-3	International Classification of Diseases for Oncology, 3rd Edition
ICRI	International Rare Cancers Initiative
ICON	International Collaborative Ovarian Neoplasm study
ICORG	Irish Clinical Oncology Research Group
ICP	intracranial pressure
ICRU	International Commission on Radiation Units and Measurements
IELSG	International Extranodal Lymphoma Study Group
IFN	interferon
IFNAR	interferon (alpha and beta) receptor
IFNGR	interferon gamma receptor
IFRT	involved-field radiotherapy
Ig	immunoglobulin
IGBT	image-guided brachytherapy
IGCCCG	International Germ Cell Consensus Collaborative Group
IGCN	intratubular germ cell neoplasia
IGF	insulin-like growth factor
IGRT	image-guided radiotherapy
IHC	immunohistochemistry
IHD	ischaemic heart disease
IL	interleukin
ILT	intraluminal brachytherapy
i.m.	intramuscular
IM	internal margin
IMN	internal mammary node
IMP	investigational medicinal product
IMRT	intensity-modulated radiation therapy
INPC	International Neuroblastoma Pathology Classification
INRT	involved node radiotherapy
IPI	International Prognostic Index
I-PSS	International Prostate Symptom Score
IQ	intelligence quotient
IR-CTV	intermediate-risk CTV

IRAS	integrated research application system
IRS	Intergroup Rhabdomyosarcoma Studies
ISO	International Organisation for Standardisation
ISH	*in situ* hybridisation
ISRT	involved-site radiotherapy
ITT	intention to treat
ITU	intensive therapy unit
ITV	internal target volume
IU	international units
i.v.	intravenous
IVC	inferior vena cava
IVU	intravenous urogram
IWG	International Working Group
JVP	jugulo-venous pressure
Ki-67	MKI67; marker of proliferation Ki-67
KIF20A	kinesin-like protein
KIT	v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog
KOC1	IGF II mRNA binding protein 3
KPS	Karnofsky performance status
KRAS	Kirsten rat sarcoma viral oncogene homolog
LACE	Lung Adjuvant Cisplatin Evaluation
LAK	lymphokine-activated killer
LAPC	locally advanced pancreatic cancer
LAR	long-acting release
LCIS	lobular carcinoma *in situ*
LCNEC	large cell neuroendocrine carcinoma
LCNED	large cell neuroendocrine differentiation
LD	latissimus dorsi
LDFS	local disease-free survival
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LDR	low dose rate
LEEP	loop electro-excision procedure
LFT	liver function tests
LGG	low-grade glioma
LH	luteinising hormone
LHRH	luteinising hormone releasing hormone
LHRHa	luteinising hormone releasing hormone agonist
LLETZ	large loop excision of the transformation zone
LMM	lentigo maligna melanoma
LN	lymph node
LOH	loss of heterozygosity
LR	local recurrence
LUCADA	National Lung Cancer Audit Database
MAb	monoclonal antibody
MAB	maximal androgen blockade
MACH-NC	Meta-Analysis of Chemotherapy on Head and Neck Cancer
MACIS	metastases, age, completeness of surgery, invasion of extrathyroidal tissues, size
MAG 3	mercaptoacetyltriglycerine
MAGE	melanoma antigen expression family
MAGIC	Medical Research Council Adjuvant Gastric Infusional Chemotherapy
MALT	mucosa-associated lymphoid tissue
MAMS	multi-arm multi-stage
MAOI	monoamine oxidase inhibitor
MAPK	mitogen-activated protein kinase
MART	melanoma antigen recognised by T cells

MASCC	Multinational Association for Supportive Care in Cancer
MBC	metastatic breast cancer
MBq	mega-Becquerel
MCF-7	Michigan Cancer Foundation-7
MCL	mantle cell lymphoma
mCRC	metastatic colorectal cancer
MDFS	metastatic disease-free survival
MDR	medium dose rate
MDT	multidisciplinary team
MEN	multiple endocrine neoplasia
MET	MET proto-oncogene, receptor tyrosine kinase (synonym = hepatocyte growth factor receptor)
MF	mycosis fungoides
M:F	male to female
MGMT	O^6 methylguanine-DNA methyltransferase
MGUS	monoclonal gammopathy of undetermined significance
MIB-1	antibody to Ki-67
MIBC	muscle-invasive bladder cancer
MIBG	meta-iodobenzylguanidine
MLC	multileaf collimator
MM	malignant melanoma
MMC	mitomycin C
MMAE	monomethyl auristan E
MMR	mismatch repair
MMS	multimodal screening
mp	multiparametric
MPHOSPH1	M phase phosphoprotein 1
MRC	Medical Research Council
MRCP	magnetic resonance cholangiopancreatogram
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRS	magnetic spectroscopy
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	median survival
MSCC	malignant spinal cord compression
MSH	DNA mismatch repair gene
MSI	microsatellite instability
MSKCC	Memorial Sloan-Kettering Cancer Center
MSTR1	macrophage-stimulating 1 receptor (c-met-related tyrosine kinase)
MSU	mid-stream urine
MTC	medullary thyroid carcinoma
MTD	maximally tolerated dose
MTOR	mechanistic target of rapamycin (serine/threonine kinase)
MUC	mucin
MUGA scan	multigated acquisition scan
MUM1	melanoma-associated antigen (mutated) 1
MUO	metastatic malignancy of unknown origin
MV	megavoltage
MW	molecular weight
MYC	v-myc myelocytomatosis viral oncogene homolog
MYCN	v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog
MYOD1	myogenic differentiation 1
MZL	marginal zone lymphoma
NAC	nipple areola complex
NAHT	neoadjuvant hormone therapy

NALP7	NLRP7; NLR family, pyrin domain containing 7
NAT	*n*-acetyltransferase
NCCN	National Comprehensive Cancer Network
NCCTG	North Central Cancer Treatment Group
NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
Nd-YAG	neodynium-doped yttrium–aluminium–garnet
NET	neuroendocrine tumour
NEU	neuro/glioblastoma-derived oncogene homolog: HER2; erb-b2 receptor tyrosine kinase 2
NF	neurofibromatosis
NHL	non-Hodgkin lymphoma
NHS	National Health Service
NI	Nottingham prognostic index
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NIHR	National Institute for Health Research
NK	natural killer
NLPHL	nodular lymphocyte predominant Hodgkin lymphoma
NM	nodular melanoma
NMIBC	non-invasive bladder cancer
n-myc	MYCN; v-myc avian myelocytomatosis viral oncogene neuroblastoma-derived homolog
NNT	number needed to treat
nocte	at night
NOS	not otherwise specified
NPC	nasopharyngeal carcinoma
NRIG	National Radiotherapy Implementation Group
NS	not significant
NSAA	non-steroidal anti-androgen
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small-cell lung cancer
NSGCT	non-seminomatous germ cell tumour
NST	no specific type
NTCP	normal tissue complication probability
NY-ESO-1	cancer/testis antigen
OAR	organs at risk
OC	oesophageal cancer; oral contraceptive
OCT3/4	POU5F1; POU class 5 homeobox 1
OFA	oncofetal antigen
OFS	ovarian function suppression
OPC	oropharyngeal carcinoma
OPT	orthopantogram
OR	odds ratio
OS	overall survival
p16	CDKN2A; cyclin-dependent kinase inhibitor 2A
p16INK4a	p16: CDKN2A; cyclin-dependent kinase inhibitor 2A
p450	cytochrome p450
PanIN	pancreatic intraepithelial neoplasia
PAP	prostatic acid phosphatase
PATCH	Prostate Adenocarcinoma: TransCutaneous Hormones
PAX8	paired box 8
PCI	prophylactic cranial irradiation
PCNSL	primary central nervous system lymphoma
PCP	*pneumocystis carinae* pneumonia

pCR	pathological complete response
PD-1	PDCD1; programmed cell death 1
PDA	poorly differentiated adenocarcinoma
PDC	poorly differentiated carcinoma
PDD	percentage depth dose
PDE5	phosphodiesterase type 5 inhibitor
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PD-L1	programmed death-ligand 1
PDN	poorly differentiated neoplasm
PDR	pulsed dose rate
PDT	photodynamic therapy
PDVR	pancreaticoduodenectomy with vein resection
PEI	percutaneous ethanol injection
PET	positron emission tomography
PFS	progression-free survival
PGF	placental growth factor
PGP	protein gene product
PgR	progesterone receptor
PhRMA	Pharmaceutical Research and Manufacturers of America
PI3K	phosphatidyl inositol 3 kinase
PICC	peripherally inserted central catheter
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PIP	Personal Independent Payment
PLAP	placental alkaline phosphatase
PLDH	pegylated liposomal doxorubicin hydrochloride
PM	partial mole
PMS	PMS1 postmeiotic segregation increased 1
PMS2	PMS2 postmeiotic segregation increased 2 (*S. cerevisiae*)
PNET	primitive neuroectodermal tumour
p.o.	*per os* (by mouth)
PORT	postoperative radiotherapy
PORTEC	PostOperative Radiation Therapy in Endometrial Cancer
PP	pancreatic polypeptide
PPPD	pylorus-preserving pancreatico-duodenectomy
PPE	palmar–plantar erythrodysaesthesia
PPI	proton pump inhibitor
PPRT	prostate and pelvic radiotherapy
PR	partial response
PR-A	progesterone receptor A
PR-B	progesterone receptor B
p.r.n.	*pro re nata* (as required)
PrRT	prostate radiotherapy
PRRT	peptide-receptor radionuclide therapy
PRV	planning organ at risk volume
PS	WHO performance status
PSA	prostate-specific antigen
PSTT	placental site trophoblast tumour
PTC	in thyroid cancer = papillary thyroid carcinoma; in hepatobiliary cancer = percutaneous transhepatic cholangiograph
PTCH	patched gene
PTEN	phosphatase and tensin homolog
PTH	parathyroid hormone
PTH-RP	parathyroid hormone-related peptide
PTV	planning target volume
PUVA	psoralen plus ultraviolet A
PV	*per vagina* (through the vagina)
PVC	poly (vinyl-choride)
PVI	protracted venous infusion
QA	quality assurance

q.d.s.	*quater die sumendum* (four times a day)
QART	Quality Assurance in Radiation Therapy
QLQ	quality of life questionnaire
qmax	maximum flow
QOL	quality of life
QT	QT interval
R0	complete resection
R1	microscopic involved margins
R2	macroscopic involved margins
RA	rheumatoid arthritis
RAF	rapidly accelerated fibrosarcoma
RAF1	Raf-1 proto-oncogene, serine/threonine kinase
RAGE	renal antigen expression family
RANK	approved gene symbol = TNFRSR11A; name = tumour necrosis factor receptor superfamily, member 11a, NFKB activator
RANKL	TNFSF11; tumour necrosis factor (ligand) superfamily, member 11
RAS	rat sarcoma viral oncogene homolog
Rb	retinoblastoma
RB1	retinoblastoma 1 (including osteosarcoma)
RBE	radiobiologically equivalent dose
RC	radical cystectomy
RCC	renal cell carcinoma
RCCM	renal cell carcinoma marker
RCR	Royal College of Radiologists
RCT	randomised controlled trial
REAL	revised European–American lymphoma
RECIST	response evaluation criteria in solid tumours
RET	ret proto-oncogene
RFA	radiofrequency ablation
RFS	recurrence-free survival
rhTSH	recombinant human thyroid-stimulating hormone
RIC	reduced intensity conditioning
RMI	relative malignance index
RON	Recepteur d'Origine Nantais: MSTR1; macrophage-stimulating 1 receptor (c-met-related tyrosine) kinase
RPLND	retroperitoneal lymph node dissection
RR	response rate; relative risk
RRA	radioiodine remnant ablation
RS	recurrence score
rT	recurrent tumour
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
S100	S100 calcium-binding protein
SAB	same as before
SABR	stereotactic ablative body radiation therapy
SACT	systemic anti-cancer therapy
SAE	serious adverse event
SBP	solitary bone plasmacytoma
SBRT	stereotactic body radiotherapy
s.c.	subcutaneous
SCC	squamous cell carcinoma
SCF	supraclavicular fossa
SCFR	mast/stem cell growth factor receptor
SCGB2A2	secretoglobin family 2A member 2 (Mammaglobin-A)
SCLC	small cell lung cancer
SCT	stem cell transplant
SDH	succinate dehydrogenase complex
SEER	Surveillance Epidemiology and End Results

SEP	solitary extramedullary plasmacytoma
SERM	selective oestrogen receptor modulator
SH	SRC homology
SI	sacro-iliac
S-I	superior–inferior
SIADH	syndrome of inappropriate antidiuretic hormone
SIGN	Scottish Intercollegiate Guidelines Network
SIOP	Société Internationale d'Oncologie Pédiatrique
SIRT	selective internal radiation microsphere therapy
SLE	systemic lupus erythematosus
SLL	small lymphocytic lymphoma
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
SM	set-up margin
SMA	smooth muscle actin
SMAD4	SMAD family member 4
SMAS	superficial musculo-aponeurotic system
SMC	Scottish Medicines Consortium
SMO	smoothened receptor
SMV	superior mesenteric vein
SNB	sentinel node biopsy
SPECT	single photon emission computed tomography
SRC	SRC proto-oncogene, non-receptor tyrosine kinase
SRH	stigmata of recent haemorrhage
SS	Sézary syndrome
SSD	source–skin distance
SSM	superficial spreading melanoma
SSP	statutory sick pay
SSRS	somatostatin receptor scintigraphy
STAT3	signal transducer and activator of transcription 3
SV 40	simian virus 40
SVC	superior vena cava
SVCO	superior vena cava obstruction
SWENOTECA	Swedish and Norwegian Testicular Cancer Group
SWOG	Southwest Oncology Group
SXR	superficial X-ray
T3	liothyronine
T4	thyroxine
TA	technology appraisal
TACE	transarterial chemo-embolisation
TAH	total abdominal hysterectomy
TB	tuberculosis
TBI	total body irradiation
TCC	transitional cell carcinoma
TCP	tumour control probability
t.d.s.	*ter die sumendum* (three times a day)
TEK	TEK tyrosine kinase, endothelial
TEM	trans-anal endoscopic microscopy
TFE3	transcription factor binding to IGHM enhancer 3
Tg	thyroglobulin
TGF-β	transforming growth factor beta
THW	thyroid hormone withdrawal
TIE2	tunica interna endothelial cell kinase: TEK; TEK tyrosine kinase, endothelial
TKI	tyrosine kinase inhibitor
TLD	thermoluminescence dosimetry
TLM	transoral laser microsurgery
TLS	tumour lysis syndrome

TME	total mesorectal excision
TMR	tissue maximum ratio
TNF	tumour necrosis factor
TNFSF11	tumour necrosis factor (ligand) superfamily, member 11
TNM	tumour nodes metastases
TORS	transoral robotic surgery
TP53	tumour protein p53
TPR	tissue phantom ratio
TRAIL	tumour necrosis factor apoptosis-inducing ligand: TNFSF10; tumour necrosis factor (ligand) superfamily, member 10
TROG	Trans Tasman Radiation Oncology Group
TRUS	transrectal ultrasound
TSC	trial steering committee
TSEBT	total skin electron beam therapy
TSH	thyroid-stimulating hormone
TTF-1	thyroid transcription factor 1
TTK	TTK protein kinase
TURBT	transurethral resection of bladder tumour
TURP	transurethral resection of the prostate
TVS	transvaginal ultrasound
U+E	urea and electrolytes
UFT	tegafur–uracil
UC	ulcerative colitits
UICC	International Union Against Cancer
UK	United Kingdom
UKINETS	UK and Ireland Neuroendocrine Tumour Society
URLC10	upregulated in lung cancer 10
US	ultrasound scan
USA	United States of America
UTI	urinary tract infection
UV	ultraviolet
VAIN	vaginal intraepithelial neoplasia
VATS	video-assisted thoroscopic surgery
VC	vomiting centre
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VHL	Von Hippel Lindau
VIN	vulval intraepithelial neoplasia
VIP	vasoactive intestinal peptide
VMAT	volumetric modulated arc therapy
VSIM	virtual simulation software
VTE	venous thromboembolism
WA	wedge angle
WAF1	cyclin-dependent kinase inhibitor
WBC	white blood cell
WBrRT	whole breast radiotherapy
WBRT	whole brain radiotherapy
WCB	Wales Cancer Bank
WCC	white cell count
WHO	World Health Organisation
WLE	wide local excision
WNT	wingless-type MMTV integration site family
wt	wild-type
WT1	Wilms tumour 1
XRT	X-ray treatment

Chemotherapy regimens

ABVD	doxorubicin, bleomycin, vinblastine, dacarbazine
AC	doxorubicin, cyclophosphamide

BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone
BEAM	carmustine, etoposide, cytarabine, melphalan
BEC	bleomycin, etoposide, carboplatin
BEP	bleomycin, etoposide, cisplatin
BOP	bleomycin, vincristine, cisplatin
BuCy	busulphan, cyclophosphamide
CAF	cyclophosphamide, doxorubicin, 5-FU
CAP	cyclophosphamide, doxorubicin, cisplatin
CAPOX	capecitabine, oxaliplatin
CAV	cyclophosphamide, doxorubicin, vincristine
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisolone
CMF	cyclophosphamide, methotrexate, 5-FU
COPDAC	cyclophosphamide, vincristine, dacarbazine, predniolone
CTD	cyclophosphamide, thalidomide, dexamethasone
CVAD	cyclophosphamide, vincristine, doxorubicin, dexamethasone
CVP	cyclophosphamide, vincristine, prednisolone
Cy	cyclophosphamide
CYVADIC	cyclophosphamide, vincristine, doxorubicin, dacarbazine
DAT	daunorubicin, ara-C (cytarabine), thioguanine
DHAP	dexamethasone, cytarabine, cisplatin
EC	epirubicin, cyclophosphamide
ECF	epirubicin, cisplatin, 5-FU
ECX	epirubicin, cisplatin, capecitabine
EMA-CO	etoposide, methotrexate, dactinomycin, cyclophosphamide, vincristine
EOX	epirubicin, oxaliplatin, capecitabine
EP	etoposide, cisplatin
EP-EMA	etoposide, cisplatin–etoposide, methotrexate, actinomycin-D
Epi-CMF	epirubicin, cyclophosphamide, methotrexate, 5-FU
ESHAP	etoposide, methylprednisolone, cytarabine, cisplatin
FAC	5-FU, doxorubicin, cyclophosphamide
FEC	5-FU, epirubicin, cyclophosphamide
FEC-T	5-FU, epirubicin, cyclophosphamide then docetaxel
FF	folinic acid, 5-FU
FOLFIRI	5-FU, folic acid, irinotecan
FOLFIRINOX	5-FU, folic acid, irinotecan, oxaliplatin
FOLFOX	5-FU, folic acid, oxaliplatin
GDP	gemcitabine, dexamethasone, cisplatin
GEMCAP	gemcitabine, capecitabine
Gem-cis	gemcitabine, cisplatin
HD-MTX	high-dose methotrexate
HD-AC	high-dose cytarabine
ICE	ifosfamide, carboplatin, etoposide
IE	ifosfamide, etoposide
IGEV	ifosfamide, gemcitabine, prednisolone, vinblastine
IVA	ifosfamide, vincristine, dactinomycin
IVADo	ifosfamide, vincristine, dactinomycin, doxorubicin
JEB	carboplatin, etoposide, bleomycin
MAP	methotrexate, doxorubicin, cisplatin
M-CAVI	methotrexate, carboplatin, vinblastine

MTX	methotrexate
MVAC	methotrexate, vinblastine, doxorubicin, cisplatin
MVP	mitomycin, vinblastine, cisplatin
OEPA	vincristine, etoposide, prednisolone, doxorubicin
OFF	oxaliplatin, folinic acid, 5FU
PEI	cisplatin, etoposide, ifosfamide
PF	cisplatin, 5-FU
PLaDo	cisplatin, doxorubicin
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
R-CVP	rituximab, cyclophosphamide, vincristine, prednisolone
R-FC	rituximab, fludarabine, cyclophosphamide
R-GCVP	rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone
R-CODOX-M/R-IVAC	rituximab, cyclophosphamide, vincristine, doxorubicin, cytarabine, methotrexate, etoposide, ifosfamide
TAC	docetaxel, doxorubicin, cyclophosphamide
TC	docetaxel, cyclophosphamide
TE-TP	paclitaxel, cisplatin; paclitaxel etoposide
TIP	paclitaxel, ifosfamide, cisplatin
TPF	docetaxel, cisplatin and 5-FU
VAC	vincristine, dactinomycin, cyclophosphamide
VACA	vincristine, dactinomycin, cyclophosphamide, doxorubicin
VAI	vincristine, dactinomycin, ifosfamide
VAIA	vincristine, dactinomycin, ifosfamide, doxorubicin
VACD	vincristine, dactinomycin, cyclophosphamide, doxorubicin
VC	vincristine, cyclophosphamide
VDC	vincristine, doxorubicin, cyclophosphamide
VEC-CDDP	vincristine, etoposide, cyclophosphamide, cisplatin
VIDE	vincristine, ifosfamide, etoposide
VIP	etoposide, ifosfamide, cisplatin
XELOX	capecitabine, oxaliplatin

Radioisotopes

^{11}C	carbon-11
^{60}Co	cobalt-60
^{51}Cr	chromium-51
^{137}Cs	caesium-137
^{18}F	fluorine-18
^{68}Ga	gallium-68
^{123}I	iodine-123
^{125}I	iodine-125
^{131}I	iodine-131
^{111}In	indium-111
^{192}Ir	iridium-192
^{177}Lu	lutetium-177
^{103}Pd	palladium-103
^{106}Ru	ruthenium-106
^{99m}Tc	technetium-99m
^{90}Y	yttrium-90

Chapter 1

Practical issues in the use of systemic anti-cancer therapy drugs

Usman Malik and Philip Savage

Introduction

The role of systemic anti-cancer therapy (SACT) in the management of cancer is evolving rapidly with widening indications for treatment and, in many diagnoses, additional therapies and lines of treatment now available. In 2015, there are now over 140 drugs licensed to be used for cancer treatment and it is not practical within this chapter to give a comprehensive description of each drug or treatment regimen. More detailed information can be found in chemotherapy textbooks, at the manufacturers' websites, the electronic Medicines Compendium (eMC) or from oncology pharmacy websites (e.g. http://www.medicines.org.uk/emc and www.bccancer.bc.ca, accessed January 2015). However, we hope this chapter, which focuses mainly on classic cytotoxic chemotherapy drugs, will provide SACT prescribers, pharmacists and administrators with sufficient information to discuss treatment with patients, to prescribe and deliver drugs safely and to recognise common treatment-related side effects.

Over the last decade there has been a major increase in activity and workloads within chemotherapy treatment units. The 2009 National Cancer Advisory Group report described an increase in overall activity of 60% in just a four year period (NCAG, 2009). This rise in activity is in part a result of increased numbers of patients but there has also been a major expansion in the indications for which there is effective treatment, the upper age range of patients treated and, in many malignancies, the number of lines of therapy available for use. Whilst the newer drugs are predominantly oral agents, the recent development of maintenance monoclonal antibody therapies for breast cancer and non-Hodgkin lymphoma and the more modern prolonged and complex regimens in gastrointestinal malignancies have added considerable pressure to the workload of pharmacy and chemotherapy treatment units.

A summary of the rapid increase in both the number of new cancer treatment drugs and the change in identity of new SACT agents can be see in Table 1.1 that shows both the historical and modern trends in new cancer drugs. This demonstrates the change from the initial cancer treatment drugs of the 1970s/80s/90s that were predominantly classic cytotoxic chemotherapy agents to a new, varied range of agents including monoclonal antibodies, TKI and MTOR inhibitors and other new agents (Savage and Mahmoud, 2013).

This increase in the number and variety of anti-cancer drugs seems set to continue as there are nearly 1000 new cancer drug trials in the USA alone at present (PhRMA, 2012). One of the consequences of the increased numbers of new drugs is the financial challenge in providing the facilities and manpower to deliver care, and to pay for the drugs themselves. This is a problem for all healthcare systems, whether paid by insurance or state-funded, and it is likely that the increasing numbers and cost of cancer drug treatment will continue to influence clinical, economic and political decision making (Sullivan *et al*., 2011).

Aims of systemic anti-cancer therapy

There are three main indications for the use of SACT drugs.

- Curative: the management of patients with chemotherapy-curable advanced malignancies including gestational choriocarcinoma, testicular cancer, ovarian germ cell tumours, acute leukaemia, Hodgkin lymphoma, high-grade non-Hodgkin lymphoma (NHL) and some rare childhood malignancies.

Practical Clinical Oncology, Second Edition, ed. Louise Hanna, Tom Crosby and Fergus Macbeth. Published by Cambridge University Press.

Table 1.1 Historical and modern trends in new cancer drugs

Drug class	Pre 1975	1975–1999	2000–2009	2010–13	Total
Cytotoxic	15	30	5	5	55
Hormonal	0	13	3	2	18
Cytokine	0	2	0	0	2
Peptide	0	2	0	1	3
MAb	0	1	5	5	11
TKI	0	0	5	6	11
MTOR	0	0	1	1	2
Other	0	0	3	0	3

The table shows the number of new cancer treatment drugs licensed during each of the time periods and the total currently available in each therapeutic class. MAb = antibody; MTOR: mechanistic target of rapamycin (serine/threonine kinase); TKI: tyrosine kinase inhibitor.

- Adjuvant: the preoperative or postoperative treatment of clinically localised malignancies, primarily breast cancer and colorectal cancer.
- Palliative: the treatment of patients with advanced incurable malignancies, where the main aims of treatment include prolonging life and reducing disease-related symptoms.

Before starting a course of SACT, the prescriber and the patient should both be clear about the aims and realistic expectations of treatment and ideally use consent forms specific to individual regimens and indications giving detailed information on the risks and benefits of treatment.

For patients with curable malignancies or receiving adjuvant therapy, it is important to avoid treatment delays or dose reductions and to maintain the calculated dose and schedule of the standard treatment protocols. The importance of this has been shown in the cure rates for testicular cancer (Toner *et al*., 2001) and lymphoma (Lepage *et al*., 1993) and also in the adjuvant treatment of breast cancer, where the rate of relapse is higher when the dose intensity is reduced (Budman *et al*., 1998).

Generally, the chemotherapy regimens used in the curable malignancies have significant side effects including neutropenia and the use of granulocyte colony stimulating factor (G-CSF) is frequently required to keep treatment on schedule. However because there is the clear intent of achieving either cure or, in adjuvant treatment, an increased chance of cure, these side effects and treatment-related risks and costs are seen as acceptable temporary issues. In contrast, for patients having non-curative chemotherapy the benefits of treatment need to be balanced against quality of life and dose reductions may be made to ensure that the patient tolerates the treatment safely.

Cytotoxic chemotherapy

Cytotoxic chemotherapy drugs aim to kill or slow the growth of tumour cells while being relatively sparing to normal non-malignant cells. The sensitivity of different tumour types to the actions of cytotoxic drugs varies widely among the cells of origin and across the range of drugs. This variation in part reflects native metabolism of the tumour cell and differing metabolic pathways, drug handling, abilities to repair DNA and sensitivity to the induction of apoptosis.

In general tumour cells are more sensitive to cytotoxic drugs than their parent cell types and also often more sensitive than the usually dose limiting cells of the bone marrow. Whilst chemotherapy treatment brings routine cures in the rare chemotherapy curable malignancies, for the common malignancies cure of metastatic disease with chemotherapy is not a realistic outcome. The ability of chemotherapy treatment to cure patients with these limited numbers of chemo curable malignancies, listed above, started in the 1950s and was firmly established by the end of the 1970s. Since then, despite many new classic cytotoxic drugs being subsequently introduced, this pattern of chemotherapy curable malignancies has not changed. Whilst there has been enormous endeavour looking at the mechanisms of chemotherapy resistance, other explanations based on the natural genetic processes occurring in the parent cells of the chemotherapy curable malignancies may offer an alternate perspective (Masters and Köberle 2003, Savage *et al*., 2009).

The action of cytotoxic chemotherapy drugs has traditionally been classified as being either 'cell-cycle specific' or 'cell-cycle non-specific.' The cycle-specific drugs, (such as the anti-metabolites methotrexate,

fluorouracil and gemcitabine) mainly interact with cells that are actively synthesising DNA in the synthesis (S) phase and so are most effective in tumours with high mitotic rates and kill more cells when given in prolonged exposures.

The cell-cycle non-specific drugs interact with cells in all parts of the cycle and can affect more slowly proliferating tumour cells. These include the alkylating agents (e.g. cyclophosphamide, bendamustine, ifosfamide) and the anti-tumour antibiotics (e.g. bleomycin, doxorubicin, epirubicin). These drugs are active in all phases of the cell cycle, and their effect is more closely related to the total dose rather than to the duration of administration.

More modern research suggests that this distinction is relatively crude and that most drugs affect both dividing and resting cells. However, it is still quite useful for predicting the side effects of chemotherapy, because the extended use of cell-cycle specific drugs can cause more neutropenia and mucosal damage, and for designing combination regimens.

Combination chemotherapy regimens

Most cytotoxic drugs were originally used as single agents and were then incorporated into clinical trials of combination chemotherapy schedules. The combination of drugs with different modes of action and patterns of toxicity led to major improvements in the treatment of testicular cancer and lymphoma and made these tumours routinely curable in the 1970s (Li *et al.*, 1960, Freireich *et al.*, 1964, DeVita *et al.*, 1970). In the adjuvant and palliative setting, combination treatments often also give enhanced results with acceptable toxicity.

The key principles for selecting the chemotherapy drugs for use in combinations include the following.

- Each drug has activity against the tumour as a single agent.
- There are no clinically important drug interactions between the agents.
- Combinations should avoid drugs of the same class or those with similar modes of action.
- The drugs should have different dose-limiting toxicities.

For example, BEP (bleomycin, etoposide, cisplatin) is now the regimen of choice for advanced testicular cancer. The drugs all have significant activity as single agents, usually with a short duration of response, and have different dose-limiting toxicities. By combining them with their different toxicities, each can be used at nearly the full single-agent dose, resulting in increased effectiveness with little extra toxicity. This combination changed advanced testicular cancer from a diagnosis with a poor prognosis to one which was routinely curable (Williams *et al.*, 1987).

The treatment of high-grade B-cell NHL is an example of the benefits of adding an additional modern drug with a completely different mode of action to an already effective regimen. After its introduction in the 1970s the combination of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) became standard treatment (McKelvey *et al.*, 1976), and subsequent trials comparing CHOP with more complex and toxic regimens showed no greater effectiveness (Fisher *et al.*, 1993). In contrast, addition of the anti-CD20 monoclonal antibody rituximab, with a different mode of action and minimal toxicity, to give the R-CHOP regimen has led to significant improvement in cure rates (Sehn *et al.*, 2005).

Chemotherapy scheduling

In some regimens the cytotoxic drugs must be given in the correct order, for example the combination of paclitaxel and carboplatin for patients with ovarian cancer. Carboplatin is a cell-cycle non-specific drug and is best given as a single bolus dose, infused over 30 minutes, because of the risk of hypersensitivity. The usual administration cycle is 28 days when used as a single agent because the myelosuppression nadir is between 14 and 21 days. Paclitaxel is cell-cycle specific and so should be given in multiple fractions over a prolonged period and is now usually given as a 3-hour infusion (ICON Group, 2002). Its nadir of myelosuppression occurs after 10 days, implying a maximum cycle length of 21 days, and so combining the two drugs presents a problem deciding what interval there should be between doses. However, studies have shown that giving paclitaxel before carboplatin appears to give some bone marrow protection and 21-day cycles do not produce unacceptable myelosuppression. However, recent trials giving paclitaxel weekly in combination with 3-weekly carboplatin, a 'dose-dense' schedule, showed greater effectiveness but more toxicity (Katsumata *et al.*, 2013).

SACT protocols and guidelines

The introduction of peer-reviewed treatment policies in the NHS has led to the development of local protocols for approved SACT regimens, which should be

familiar to all the health professionals who prescribe, dispense and administer them. 'Off-protocol' regimens should generally not be prescribed unless there is good evidence in the research literature.

Electronic prescribing systems for SACT have reduced the risk of prescribing errors, improved administration scheduling and provided accurate data on prescribing patterns (Ammenwerth *et al.*, 2008).

Dose calculation

Body surface area

Ideally, calculating the appropriate dose of a cytotoxic drug would take into account its pharmacokinetic properties – how the body delivers the drug to its site of action and the patient's metabolism and excretion. The dose could then be adjusted according to the toxicity seen in each patient. Although this method of chemotherapy drug dosing has been advocated, routine cytotoxic chemotherapy doses continue to be calculated according to the patient's body surface area (BSA) (Veal *et al.*, 2003).

There are several formulae for calculating BSA. The most commonly used is that of DuBois and DuBois, which dates from 1916 and was based on data from only eight adults and one child (DuBois and DuBois, 1916). Other formulae using both electronic and manual methods (nomograms and slide rules) are available, and there is generally good correlation between them.

Dose capping

Whether to dose chemotherapy according to the patient's actual weight or their calculated ideal body weight is controversial (Hall *et al.*, 2013). Using the calculated BSA in large or obese patients may lead to relative overdosing and a risk of increased toxicity. Placing an upper limit on the dose has been suggested and some centres will use 2.2 m^2 as an upper limit of BSA for curative and adjuvant treatments and 2.0 m^2 for palliative treatments. However, when prescribing for tall but non-obese individuals there is a potential risk of underdosing if the BSA is capped at 2.2 m^2. The only commonly agreed exception is in the use of vincristine, for which the dose is usually capped at 2 mg. At present there is no consensus on this, and local policies should always be checked, especially when treating patients with chemotherapy-curable tumours.

Area under the curve dosing

Carboplatin is excreted unchanged by the kidneys and is the only commonly used agent for which the dose is calculated from the renal function. A formula (the Calvert equation) has been developed based on renal function (Calvert *et al.*, 1989) by which the desired AUC (area under the curve of serum levels against time) is chosen, and the dose is calculated by the following formula:

$$\text{Dose (mg)} = \text{desired AUC} \times (\text{GFR mL/min} + 25)$$

GFR is the glomerular filtration rate, which may be calculated by ^{51}Cr-EDTA clearance, using a 24-h urine collection, or from the Cockcroft–Gault equation which derives it from a measure of serum creatinine, weight, age and sex. It is important to know which value of BSA is used in routine reporting of GFR and whether the value relates to the actual body size or to a standardised 1.73 m^2 BSA.

Body weight dosing

Body weight alone is not sufficent for calculating doses of most cytotoxic drugs except for some of the newer drugs, such as trastuzumab.

Flat dosing

Bleomycin is the only commonly used cytotoxic drug for which a fixed dose is used routinely. In the BEP regimen a fixed dose of 30,000 units on days 1, 8 and 15 is used irrespective of the patient's size. Also, many of the new SACT agents, particularly the TKI and MTOR drugs (see Chapter 2) are generally used at a standard flat dose irrespective of the patient's size and age.

Dose reduction

It is important to avoid unnecessary routine dose reductions solely on the basis of transient toxicity, particularly in curative and adjuvant treatments. Most modern protocols and clinical trial publications give clear advice on how best to reduce doses either across the regimen or for individual drugs in response to excess toxicity and using these can help maintain optimal care.

Elderly patients

Appropriately used chemotherapy can bring similar benefits in the elderly as in younger patients. However, the elderly metabolise drugs more slowly and are less resistant to side effects or complications. Whilst it is