Problem Solving in Oncology

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CLINICAL PUBLISHING

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CLINICAL PUBLISHING
OXFORD

CLINICAL PUBLISHING
an imprint of Atlas Medical Publishing Ltd

Oxford Centre for Innovation
Mill Street, Oxford OX2 0JX, UK

Tel: +44 1865 811116
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E mail: info@clinicalpublishing.co.uk
Web: www.clinicalpublishing.co.uk

Distributed in USA and Canada by:
Clinical Publishing
30 Amberwood Parkway
Ashland OH 44805 USA

tel: 800-247-6553 (toll free within U.S. and Canada)
fax: 419-281-6883
email: order@bookmasters.com

Distributed in UK and Rest of World by:
Marston Book Services Ltd
PO Box 269
Abingdon
Oxon OX14 4YN UK

tel: +44 1235 465500
fax: +44 1235 465555
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First published 2008

A catalogue record for this book is available from the British Library

ISBN 978 1 904392 84 2
Electronic ISBN 978 1 84692 576 4

Project manager: Gavin Smith, GPS Publishing Solutions, Herts, UK
Typeset by Phoenix Photosetting, Chatham, UK
Printed by TG Hostench S. A., Barcelona

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Preface

It is not difficult to assemble facts and figures about any aspect of cancer care or science these days. Five minutes at a keyboard can produce notable abstracts concerning any topic. Some excellent textbooks, of intellectual and physical weight, are found on most oncologists' bookshelves. So why write a book on problem solving in oncology? The answer lies in the need for individuals to assimilate information quickly and easily synthesize in a form to make it relevant to the problems that they meet in their everyday professional clinical activities. Many electronic and textbook sources are excellent at providing a particular piece of information but may not set it in the context of real-life clinical cases.

Problem Solving in Oncology has been written to provide the current evidence on a topic, brought together in a clinically relevant real-life, case-based format. It has been developed to serve the needs of both trainees in oncology and practising consultants. Each chapter has been developed by an interplay between an oncology trainee and an established consultant and the breadth of the topics covers most, but not all, aspects of oncology. Each chapter relates to the sort of cases which oncology professionals see every day and brings recent evidence on management to bear upon that case. Individual chapters can be read quickly and easily and serve both for education and training and to update the reader. We have kept the book small enough and short enough to be carried around, recognizing that reading of this kind will often be done on trains and planes and at home.

The editorial team is drawn from leading cancer centres in the UK and Ireland which combine large clinical practices with internationally recognized expertise in both biomedical sciences and patient-centred research. We hope that readers will find this book a uniquely useful resource to support them in their training and professional development in an enjoyable and accessible way.

The Editors
October 2007

Acknowledgements

The editors and authors warmly acknowledge the support they have received in preparing this book. Nicole Goldman collated and oversaw the book's preparation, organized and formatted it. Yvonne Doyle supported Dr O'Donnell in her work. Dr Fiona Hicks advised on the chapters on palliative care and Dr Louise Hanna on the brain tumour chapter. Finally, Jane Pennington and Clinical Publishing were patient and helpful publishers whose vision for the series of *Problem Solving* books guided and stimulated us and without whose help the book would never have been written.

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Abbreviations

3D-CRT three-dimensional conformal radiotherapy
5-HIAA 5-hydroxyindoleacetic acid
5-HT_3 5-hydroxytryptamine
AC Adriamycin and cyclophosphamide
ACC adrenal cortical carcinoma
ACIS automated cellular imaging system
ACTH adrenocorticotropic hormone
ADT androgen deprivation treatment
AFP α-fetoprotein
AJCC American Joint Committee on Cancer
ALPI Adjuvant Lung Cancer Project Italy
ANC absolute neutrophil count
ANITA Adjuvant Navelbine International Trialists Association
ASC active supportive care
ASCO American Society of Clinical Oncology
ASTRO American Society for Therapeutic Radiology and Oncology
AUC area under the curve
BEP bleomycin, etoposide and cisplatin
BSO Bilateral salpingo-oophorectomy
CAB complete androgen blockade
CALGB Cancer and Leukaemia Group B
CBOP carboplatin, bleomycin, vincristine and cisplatin
CBR clinical benefit response
CEA carcinoembryonic antigen
CF cisplatin and 5-fluorouracil
CGA comprehensive geriatric assessment
CHOP cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine], and prednisone
CHR carboplatin hypersensitivity reaction
CISCA cisplatin, cyclophosphamide and doxorubicin
CK cytokeratin
CMF cyclophosphamide, methotrexate and fluorouracil
CNS central nervous system
CSA cryosurgical ablation
CSF cerebrospinal fluid
CT computed tomography
CTZ chemoreceptor trigger zone
CVC central venous catheter
DMSO dimethylsulphoxide
DRE digital rectal examination
DTIC dacarbazine
EBRT external beam radiotherapy
ECF epirubicin, cisplatin and 5-fluorouracil
ECG electrocardiogram
ECOG PS Eastern Cooperative Oncology Group performance score
ECX epirubicin, cisplatin and capecitabine
EDTA ethylenediamine tetraacetic acid
EGFR epidermal growth factor receptor
ELND elective lymph node dissection
EMA/CO etoposide, methotrexate, dactinomycin, cyclophosphamide and vincristine
EOF epirubicin, oxaliplatin and 5-fluorouracil
EORTC European Organisation for Research and Treatment of Cancer
EOX epirubicin, oxaliplatin and capecitabine
EP/EMA etoposide, cisplatin, methotrexate and dactinomycin
ER oestrogen receptor
ERCP endoscopic retrograde cholangiopancreatography
FAC fluorouracil, doxorubicin and cyclophosphamide
FAMTX 5-fluorouracil, doxorubicin and methotrexate
FE(50)C fluorouracil, epirubicin and cyclophosphamide
FIGO International Federation of Gynecology and Obstetrics
FISH fluorescence *in-situ* hybridization
FNA fine needle aspiration
G-CSF granulocyte-colony stimulating factor
GFR glomerular filtration rate
GIST gastrointestinal stromal tumour
GITSG Gastrointestinal Tumor Study Group
GM-CSFs granulocyte macrophage-colony stimulating factors
GP general practitioner
GTN gestational trophoblastic neoplasia
Hb haemoglobin
hCG human chorionic gonadotrophin

hCSF haemopoietic colony-stimulating factor
HD high dose intensity
HGG high-grade glioma
HIFU high frequency ultrasound
HR hazard ratio
IALT International Adjuvant Lung Cancer Trial
ICC interstitial cells of Cajal
IGCCC International Germ Cell Consensus Classification
IGCCCG International Germ Cell Cancer Collaborative Group
IL interleukin
IMRT intensity-modulated radiation therapy
IV intravenous
LACE Lung Adjuvant Cisplatin Evaluation
LDH lactate dehydrogenase
LVEF left ventricular ejection fraction
MASCC Multinational Association of Supportive Care in Cancer
MEA methotrexate, etoposide and dactinomycin
MRC Medical Research Council
MRCP magnetic resonance cholangiopancreatography
MRI magnetic resonance imaging
MSCC metastatic spinal cord compression
MVAC methotrexate, vincristine, doxorubicin and cisplatin
MUGA multiple gated acquisition scan
NCCN National Comprehensive Cancer Network
NCIC National Cancer Institute of Canada
NHS National Health Service
NK-1 neurokinin-1
NPC nasopharyngeal carcinoma
NSABP National Surgical Adjuvant Breast and Bowel Project
NSAID non-steroidal anti-inflammatory drug
NSCLC non-small cell lung cancer
NSE neurone-specific enolase
NSGCT non-seminomatous germ cell tumour
OGD oesophagogastroduodenoscopy
PCV procarbazine, lomustine and vincristine
PD progressive disease
PDGFR platelet-derived growth factor receptor
PET positron emission tomography
PFS progression-free survival
PR progesterone receptor
PSA prostate-specific antigen
PSTT placental site trophoblastic tumour
PTCA percutaneous transhepatic cholangiography
RCC renal cell carcinoma
RECIST Response Evaluation Criteria in Solid Tumours
RFA radiofrequency ablation
rHuEPO recombinant human erythropoietin
RPLND retroperitoneal lymph node dissection
RR relative risk
RT radiotherapy
RTOG Radiation Therapy Oncology Group
SAGE serial analysis of gene expression
SLN sentinel lymph node
SMA smooth muscle actin
SNB sentinel node biopsy
SWOG Southwest Oncology Group
TAC docetaxel, doxorubicin and cyclophosphamide
TCC transitional cell carcinoma
TIA transient ischaemic attack
TIP paclitaxel, ifosfamide and cisplatin
TNF tumour necrosis factor
UFT uracil and tegafur
UKP unknown primary
VEGF vascular endothelial growth factor
VIP vinblastine, etoposide and cisplatin
WCC white cell count
WLE wide local excision

Chemotherapy

PROBLEM

1 Chemotherapy: Response Assessment

Case History

A patient has completed a course of chemotherapy and attends for the results of their post-treatment computed tomography (CT) scan. The reports reads: In the thorax, both previously noted metastatic deposits have reduced in size. The right mid-zone lesion now measures 4.5 cm by 2 cm compared with 5 cm by 3.5 cm previously. The left apical nodule which was previously 7 mm by 5 mm is no longer seen. However, in the upper abdomen, a 2 cm lesion is now noted in the liver, which was not scanned in the previous investigation.

How do you evaluate the patient's response to chemotherapy?

How do the methods apply to the patient?

What will you say to the patient?

Background

How do you evaluate the patient's response to chemotherapy?

Response to chemotherapy in a patient with metastatic disease can be assessed by several approaches. These include subjective and objective methods of assessing disease response. When a patient is started on treatment it is important at the outset to ascertain

how their disease will be monitored, taking into consideration the method of monitoring (which may be a combination of methods), the frequency of monitoring, and the implication of the results for further management.

Clinical assessment

Patients receiving chemotherapy will have regular clinical reviews prior to, during and following completion of their chemotherapy. These reviews provide an opportunity to assess clinically the patient's response to their treatment. The patient can be asked about symptomatic improvement which may have occurred following completion of chemotherapy, for example, pain, anorexia, breathlessness, fatigue. There is a possibility of bias in both the patient's reporting of their condition and the interpretation of the information by the physician.

Scoring systems have been developed to try to standardise assessment of clinical response. These were initially developed for use in clinical trial settings but are now commonly used in medical practice, for example, the scoring systems used to assess performance status of patients. Commonly used tools are the Karnofsky score and the World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance score (see Appendix 1.1).

In clinical studies, quality of life of patients has also been evaluated when determining response to treatment. Studies have shown that there is often a significant correlation between quality of life reported by the patient, symptom improvement and objective tumour regression.[1] Assessment with scoring systems can be a valuable means of monitoring patient response. Routine use in clinical practice may sometimes be difficult as time during a consultation is often limited, and patients may find it difficult to complete the sometimes complex questionnaires. Studies, however, have shown that the integration of quality-of-life questionnaires in routine practice is feasible, and has a positive impact on patient–doctor communication and the patient's functional and emotional wellbeing.[2]

Clinical examination also may provide a means of monitoring response to treatment. Direct measurement of palpable tumour masses may be possible in some cases, e.g. lymphadenopathy. When describing lesions, the site, size and appearance should be noted as accurately as possible to reduce intra-observer variability. Clinical photography can also be a useful means of monitoring disease response where exact tumour dimensions are difficult to ascertain or multiple lesions are present, e.g. inflammatory breast cancer. It allows for accurate documentation of disease, and provides a useful tool for comparison of lesions before and after treatment.

Biochemical tumour markers

Tumour markers are substances which are either released directly by a tumour or are released by normal tissue in response to the presence of a malignant tumour. These substances can be antigens, proteins, enzymes, hormones or other molecular substances. Their role in clinical practice varies. For example, prostate-specific antigen (PSA) is widely used to monitor disease and is under investigation as a screening marker, whereas other markers such as carcinoembryonic antigen (CEA) can be used to detect disease recurrence. Some of the most commonly used tumour markers are shown in Table 1.1, along with benign causes of elevation and their sensitivities.

Table 1.1 Commonly used tumour markers

Marker	Associated malignancy	Benign conditions	Sensitivity (%)
CA27.29	Breast	Breast, liver and kidney disorders	33 – early stage
			67 – late stage
CEA	Colonic	In smokers, peptic ulcer disease, ulcerative colitis, Crohn's disease	25 – early stage 75 – late stage
CA19.9	Pancreatic and biliary tract	Pancreatitis, cirrhosis	80–90 – in pancreatic
AFP	Hepatocellular and non-seminomatous germ cell tumours	Viral hepatitis, cirrhosis, pregnancy	80 – in hepatocellular
βhCG	Non-seminomatous germ cell tumours	Hypogonadal states, marijuana use	20 – early stage 85 – late stage
CA125	Ovarian	Pregnancy, ascites, cirrhosis	50 – early stage 85 – late stage
PSA	Prostate	Prostatitis, benign prostatic hypertrophy	75 – in organ confined disease

hCG, human chorionic gonadotrophin; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; PSA, prostate-specific antigen.

Tumour markers can be used to assess response to chemotherapy. The rate of fall of the tumour markers can used to determine response to treatment, for example in the treatment of germ cell tumours. Studies have shown that normalization of α-fetoprotein (AFP) and β-human chorionic gonadotrophin (βhCG) in patients with germ cell tumours corresponds to complete remission with chemotherapy and survival.[3]

In ovarian cancer, studies have shown that defined responses of CA125 may be used as a means of assessing tumour response, and that this is as reliable as serial CT scanning of patients known to be CA125 responders.[4] The definition of what numerical change in the CA125 level is classed as a response is debatable, with several definitions having been proposed. One example, which has been validated, is that serial increases of 25% in four samples, 50% in three samples or levels persistently elevated at more than 100 μ/ml related to disease progression.[5] For this to be used in clinical practice to maintain accuracy it is necessary to use a computer program, which is not always feasible in routine clinical practice. Simpler definitions have been developed, for example a confirmed doubling of the CA125 from the nadir predicted progression with a sensitivity of 94% and specificity of almost 100% in patients on second-line chemotherapy.[6]

As there is ongoing debate with regard to the defined role of tumour markers, in practice tumour markers are often used in adjunct to clinical and radiological indices of tumour response. Inter-centre variation in the measurement of tumour markers can also cause difficulty in the interpretation of markers as these techniques are as yet not fully standardized.

Radiological assessment

The most commonly used method of assessing tumour response in the clinical setting is radiological assessment. Comparison between pretreatment and mid or post-treatment scans can provide evidence of response to chemotherapy. The modality used depends on

which marker lesion is being followed to monitor response to treatment. Where possible, plain radiographs or ultrasound is preferable as their use reduces the amount of ionizing radiation to which a patient is exposed; also in most centres they are more easily accessible.

Plain films are quick and simple to obtain and can be interpreted by non-radiologists. The information gained from them can be useful in determining response to treatment, for example in lung lesions in non-small cell lung cancer. However, the information is often limited. Ultrasound again is readily available but is operator dependent, which can introduce inaccuracy in the tumour measurement and make serial imaging difficult to interpret. The reproducibility of these methods is not as accurate as that of CT and magnetic resonance imaging (MRI). Therefore it may be necessary to perform assessment by CT or in some cases MRI to accurately assess disease response.

In an effort to standardize assessment of tumour response both in trial and non-trial settings, Response Evaluation Criteria in Solid Tumours (RECIST)[7] were developed in 2000, providing uni-dimensional criteria for tumour assessment. RECIST replaced the 1981 WHO criteria for tumour response[8] which had originally been developed mainly for use in relation to plain radiographs and early CT scanning, and used bi-dimensional criteria. RECIST criteria also define the use of tumour markers and clinical findings in the assessment of tumour response, although the main focus is on the radiological assessment of tumours. RECIST criteria categorizes lesions into:

- **Measurable lesions** – lesions that can be accurately measured in at least one dimension with the longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.
- **Non-measurable lesions** – all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e. bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis, cystic lesions, and also abdominal masses that are not confirmed.

Following identification of these baseline lesions a maximum of five lesions per organ or ten lesions in total are identified as target lesions. The sum of the longest diameters of the target lesions is then calculated. The response to treatment is determined by the serial assessment of these lesions. Table 1.2 shows the definitions of response according to RECIST criteria for target lesions and Table 1.3 shows definitions for non-target lesions.[9] RECIST is the most commonly used tool for assessing disease response. It provides standardized definitions of response in the setting of clinical trials, although its use in routine clinical practice is perhaps less structured.

Table 1.2 Definitions of response of target lesions

Complete response (CR)	Disappearance of all target lesions
Partial response (PR)	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Table 1.3 Definitions for non-target lesions

Complete response	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete response/ stable disease	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Discussion

How do the methods apply to the patient?

The case history above is an example of where structured tools used routinely in trials are difficult to apply in routine clinical practice. There is one measurable lesion, the right mid-zone mass (the target lesion), and one non-measurable lesion, the left apical nodule (the non-target lesion), on the pre-treatment scan. By RECIST criteria the post-treatment scan shows stable disease of the target lesion as the maximum longitudinal diameter has reduced by 10%. The non-target lesion has resolved fully indicating complete response (although no tumour marker information is given). The presence of the new lesion in the liver in this case would not affect the best overall response, as the liver has not been imaged previously so there is the possibility that the lesion was present beforehand and it is unknown if it has altered with treatment. To determine best overall response both responses are taken into account (Table 1.4), and the patient would be said to have stable disease by RECIST.

If the WHO criteria are applied the outcome would differ from that of RECIST. WHO uses the sum of the products of the longitudinal and perpendicular measurements of the lesions, and does not specify a maximum number of lesions to be included in the assessment. In this example assessment of response by WHO would conclude that the patient had achieved a partial response. This highlights the need for standardization of response criteria, especially where comparison is being made between outcome measures, i.e. in multicentre clinical trials.

Table 1.4 Assessing response with RECIST

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease.

The example also illustrates the need to take into account all indices of response. If the patient felt their symptoms had reduced in this case, one would be more inclined to think that the patient had a partial response to their treatment.

What will you say to the patient?

The case demonstrates the difficulty in relaying information to patients. It is important to try to inform the patient fully and clearly about their condition from the outset. In this case the patient may see the new information with regard the liver metastases as being an indication of deterioration of their condition, when this may not necessarily be the case.

When discussing post-treatment results with patients, spend time going through results, explaining the implications of results and their impact on future management and addressing any questions that the patient may have.

Conclusion

Assessment of tumour response is a complex process which involves the use of several modalities. The decisions made on the basis of these results have direct implications for patient care.

Tumour assessment is an area which will continue to become more complex. The development of new targeted agents has meant that present evaluation methods for tumour response are likely to be insensitive to these agents. This has led to the development of new molecular and radiological biomarkers which aim to determine more accurately the response of tumours to therapeutic intervention. These new methods will no doubt be translated into routine clinical practice in the future.

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Appendix 1.1

Appendix Table 1.1 Karnofsky performance score

100	Normal, no signs or symptoms
90	Minor signs or symptoms
80	Activity with effort, signs and symptoms present
70	Activity restricted, not working, self-caring, lives at home
60	Requires some help
50	Frequent medical care and help
40	Disabled
30	In hospital, death not near
20	Hospitalized and supported
10	Moribund
0	Dead

Appendix Table 1.2 WHO/ECOG performance scores. KP, Karnofsky performance score

0	Able to carry out all normal activity without restriction	KP: 100
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work	KP: 80, 90
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours	KP: 60, 70
3	Capable only of limited self-care; confined to bed or chair more than 50% of waking hours	KP: 40, 50
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair	KP: 20, 30