CHAPTER 1

Introduction to clinical problems in oncology

Sing Yu Moorcraft
The Royal Marsden NHS Foundation Trust, UK

CHAPTER MENU

Cancer is currently a major healthcare problem. For example, in the UK, approximately 33% of the population will develop some form of cancer during their lifetime. A person's risk of developing cancer is dependent on age and therefore the importance of oncology is likely to grow even further in the coming decades as the average age of the population increases. Oncology is one of the fastest developing specialities in medicine, with increasingly complex treatments entering daily practice and a significant number of patients in clinical trials. In the UK, the specialty is comprised of clinical oncology and medical oncology. The main difference is that clinical oncologists deliver radiotherapy, while medical oncologists do not and have historically been more heavily involved in drug research and clinical trials.

Patients may present to their oncology team, local hospital, A&E or GP with symptoms due to their cancer (e.g. pain), secondary complications (e.g. bowel obstruction) or side effects from their treatment. This book aims to provide practical guidance on how to manage the most commonly occurring problems experienced by oncology patients. However, this book is not designed to replace local or national guidelines and patients who require admission to hospital should be discussed with their oncology team or the acute oncology team in accordance with local procedures.

Clinical Problems in Oncology: A Practical Guide to Management, First Edition.
Edited by Sing Yu Moorcraft, Daniel L.Y. Lee and David Cunningham.

General approach to the management of oncology patients

Types of treatment

Oncology treatments can be local or systemic. Local treatments include surgery and radiotherapy. Systemic treatments include chemotherapy, endocrine treatments, immunotherapy and targeted therapies (e.g. monoclonal antibodies or small molecules which target specific receptors or cell signalling pathways).

This book provides guidance on the management of toxicities associated with oncology treatment. It is important to consider the aims of treatment when deciding on the most appropriate management strategy. The aims of treatment can be:

- *Curative*: treatment given as the definitive treatment for cure.
- *Radical*: usually refers to chemotherapy or chemoradiotherapy given with curative intent.
- *Neoadjuvant*: treatment given before a definitive treatment with the aim to facilitate the procedure and/or improve the chances of curing the patient.
- *Adjuvant*: treatment given after a definitive treatment, with the aim to reduce the risk of recurrence (and therefore increase the chances of curing the patient) by destroying micrometastatic disease.
- *Palliative*: the aims of treatment are to improve patients' symptoms and quality of life. The treatment may (but not necessarily) prolong the patient's life and will not cure the patient.

The management of toxicities should be discussed with the patient's oncology team, but in general, if a patient is receiving treatment with curative intent, it is important to try to minimise dose delays and reductions, whenever possible, to maintain treatment efficacy. However, in patients receiving palliative treatment, quality of life is the most important consideration.

Tumour types and extent of disease

In oncology, treatment decisions are often heavily influenced by both the type and extent of a patient's tumour. This involves grading and staging their disease.

- *Grading*: the grade of a tumour gives an indication of how well differentiated a tumour is. This often reflects the aggressiveness of the tumour, with grade I being the most differentiated and grade IV being the least differentiated.
- *Staging*: staging is used to assess the extent of disease. Some cancers have their own specialised staging systems, but many are staged by the TNM staging system. In TNM staging, the T usually represents tumour size or depth, the N reflects nodal involvement (which may be number of nodes, size of nodes or pattern of nodal involvement) and the M indicates the presence or absence of metastatic disease.

Some cancers have a predictable pattern of nodal spread and therefore some patients undergo a sentinel lymph node biopsy to determine the presence of nodal involvement. The sentinel node is the first lymph node that a cancer drains to and if it is clear of tumour then it is unlikely that lymph nodes further down the chain are involved.

Other important tumour characteristics

- *Hormone/endocrine sensitivity*: some cancers, such as breast cancer, can be hormone sensitive.
- *Increased receptor expression*: some cell surface receptors are overexpressed in certain cancer cells, for example HER2 positive breast or gastric cancers.
- *Presence or absence of specific mutations*: specific mutations have been linked to the development/progression of cancer. These mutations can be targeted by drugs, for example vemurafenib for BRAF mutation positive metastatic melanoma.

Decision making in cancer patients

Decision making in cancer patients can be complex. The following questions provide a framework to aid in making these decisions.

1 What is the histology/type of cancer? i.e. 'what is it?'
This impacts on prognosis and treatment, for example some types of cancer are sensitive to radiotherapy (e.g. squamous cell carcinomas), whereas others are relatively radiation resistant.

2 What is the stage of their cancer? i.e. 'where is it?'
- **(a)** This also impacts on prognosis and treatment.
- **(b)** In general, localised disease is treated with local therapies, whereas systemic disease is treated with systemic agents.

3 Is it potentially curable (based on tumour histology and staging)?

4 If we could potentially cure their cancer, what would the treatment involve? (e.g. surgery +/− chemotherapy +/− radiotherapy).
- **(a)** Would neoadjuvant therapy be beneficial?
  Neoadjuvant therapy may increase the chance of cure if the patient responds to treatment (e.g. by shrinking a tumour so that it can be surgically removed with clear margins). However, there is a risk of the patient's cancer progressing if they do not respond to neoadjuvant therapy.
- **(b)** Would adjuvant therapy be beneficial?
  This is often a complicated decision as the patient has already had a radical treatment aiming for cure. This treatment alone may have cured the patient. However, some patients will be cured by the addition of adjuvant treatment.

  The individual patient will not know if they personally benefited from the adjuvant treatment as the benefit is determined from population statistics. There is no biochemical or radiological evidence to show an immediate benefit of treatment.

This can be difficult to explain to patients and the choice of statistics used to explain benefits and risks can influence their decisions regarding treatment.

Decision-making aids (such as www.adjuvantonline.com) can assist with decision making and explanations.

Factors to consider when making decisions regarding adjuvant therapy include:

The presence of risk factors for local recurrence, for example large tumours, close surgical margins, nodal involvement. Adjuvant radiotherapy may be indicated for these patients.

The presence of risk factors for haematogenous spread, for example high grade tumours, lymphovascular invasion, nodal involvement. Adjuvant chemotherapy may be appropriate to reduce the risk of developing metastatic disease.

The pattern of lymphatic spread:

(i) If this is predictable then radiotherapy may be appropriate to eradicate subclinical disease in the next echelon of nodes.

(ii) If this is not predictable then systemic therapy is more appropriate.

(c) What are the potential side effects and complications of treatment?

(d) Is the patient fit enough for treatment? Consider age and comorbidities.

(e) What are the patient's priorities?

(i) Different patients have different views on treatment. Some patients would prefer to have a treatment with a small chance of cure but significant side effects, whereas for others their quality of life is more important.

(ii) It is important to balance the potential benefits of treatment with both the short and long-term side effects and risks. This is particularly important when considering adjuvant therapies.

5 If the cancer is not curable (either due to the disease itself or due to the patient's suitability for curative treatment), what are the aims of possible treatment options? For example, symptom control, slowing of disease progression, prevention of complications.

(a) What would the treatment involve?

(b) What is the likely response rate/improvement in survival?

(c) What are the potential side effects and complications of treatment?

(d) Is the patient fit enough for treatment? Consider age and comorbidities.

(e) What are the patient's priorities?

(i) It is important that the patient understands the potential benefits and risks of treatment. Their initial expectations may not be realistic and may alter following an informed discussion.

(ii) Different patients have different views on treatment. Some patients would prefer to have a treatment with a small chance of response and a small improvement in overall survival but significant side effects, whereas for other patients their quality of life is more important.

Assessing response to treatment

There are a number of different ways of assessing whether a patient is responding to a treatment. If the patient has clinically measurable disease (e.g. a breast lump) then this can be regularly measured and compared to previous measurements. Some cancers have tumour markers that correlate with response to treatment, for example PSA in patients with prostate cancer. In other patients, response assessment involves imaging (e.g. with CT scans, bone scans, PET scans). There are defined criteria for the radiological assessment of response, such as the RECIST 1.1 criteria (Response Evaluation Criteria In Solid Tumours). This assesses both target lesions and non-target lesions:

- *Target lesion* = a lesion that can be accurately measured in at least one dimension with a longest diameter that is ≥ 10 mm with CT or ≥ 20 mm by chest X-ray.
- *Non-target lesion* = all other lesions, including small lesions, for example leptomeningeal disease, ascites, pleural and pericardial effusions.

RECIST 1.1 criteria for evaluation of target lesions

- *Complete response (CR)* = disappearance of all target lesions. Any pathological lymph nodes must have a reduction in short axis to < 10 mm.
- *Partial response (PR)* = at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- *Stable disease (SD)* = neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters.
- *Progressive disease (PD)* = at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum diameter recorded since the treatment started (the sum must also demonstrate an absolute increase of at least 5 mm) or the appearance of one or more new lesions.

RECIST 1.1 criteria for evaluation of non-target lesions

- *Complete response (CR)* = disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- *Incomplete response/stable disease (SD)* = persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits.
- *Progressive disease (PD)* = appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

References

Cancer Research UK. All cancers combined Key Facts. Available from: http://info.cancerresearchuk.org/cancerstats/keyfacts/Allcancerscombined/ (accessed 1 January 2014).

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European Journal of Cancer*. 2009. 45(2): 228–47. Epub 23 December 2008.

Table 1.1 Performance status.

Score (%)	Karnofsky performance status	Score	WHO/ECOG performance status
100	Normal, no signs of disease.	0	Asymptomatic, fully active and able to carry out all pre-disease activities without restriction.
90	Capable of normal activity, a few symptoms or signs of disease.	1	Symptomatic, restricted in physically strenuous activity but ambulatory and able to carry out light or sedentary work.
80	Normal activity with some difficulty. Some symptoms or signs.		
70	Self-caring, not capable of normal activity or work.	2	Capable of all self-care but unable to carry out any work activities; < 50% in bed during the day.
60	Needs some help with care; can take care of most personal requirements.		
50	Help required often, frequent medical care needed.	3	Capable of only limited self-care; > 50% in bed during the day.
40	Disabled, requires special care and help.		
30	Severely disabled, hospital admission needed but no risk of death.	4	Completely disabled and cannot do any self-care. Totally confined to bed or chair.
20	Very ill, needs urgent admission and requires supportive care.		
10	Moribund, rapidly progressive fatal disease.		
0	Death.	5	Death.

Adapted from Ma C, *et al*. *European Journal of Cancer*. (2010). 46: 3175–83. Reproduced with permission of Elsevier.

Performance status

Performance status (PS) is used to try to quantify patients' physical well-being and help guide treatment decisions. PS should be routinely documented for all oncology patients. There are a number of scoring systems in use (see Table 1.1).

Tumour markers

Overview

- Tumour markers are substances, usually proteins, which are produced by cancer cells or normal tissues in response to cancer growth.
- Some are relevant to one type of cancer, others to a number of different cancers.
- Tumour markers can also be elevated by non-cancerous conditions and are therefore not used on their own to diagnose cancer.

- Not all patients with cancer have elevated tumour markers and so a negative result does not necessarily exclude the presence of cancer.

Current uses of tumour markers

- *Screening*: their role in screening programmes is not fully established due to low specificity and/or low levels seen at early stages of disease.
- *Monitoring of high risk patients*: they may be useful in the monitoring of patients who are at particularly high risk of specific cancers due to a strong family history/gene mutations.
- *Diagnosis*: they can *assist* with diagnosis and guide further investigations (e.g. an elevated Ca125 might be suggestive of ovarian cancer rather than other pathology).
- *Staging*: they can have a role in staging tumours to assess the extent of disease (e.g. elevated LDH is part of the staging system for melanoma).
- *Determining prognosis*: they can be an indicator of a patient's prognosis.
- *Assessing response to treatment/monitoring for disease recurrence*: if a patient has elevated markers, then the markers can be used to assess response to treatment and to monitor for signs of treatment resistance and disease progression (i.e. if the level drops then this is suggestive of a response to treatment, if the level then starts rising again then the treatment may be losing efficacy). If a patient did not have elevated markers prior to treatment then they cannot be used to assess response.

Common tumour markers

New potential tumour markers are constantly being evaluated and incorporated into clinical practice. Table 1.2 provides a guide to the most commonly used tumour markers. A full discussion of the use of specific markers in each cancer type is beyond the scope of this book.

Tumour markers most commonly measured for specific cancers

- *Breast*: Ca15-3, CEA, Ca125
- *Colon*: CEA, Ca19-9
- *Germ cell*: AFP, LDH, hCG
- *Hepatocellular*: AFP
- *Ovarian*: Ca125, CEA
- *Prostate*: PSA
- *Upper GI/pancreatic*: Ca19-9, CEA

Circulating tumour cells/DNA

- Circulating tumour cells are tumour cells that are found in the peripheral circulation in low concentrations. These cells have potential as markers of response to treatment, assessment of prognosis and monitoring for recurrence.
- Circulating tumour DNA is cell-free DNA carrying tumour specific alterations. This DNA is found in the peripheral circulation and has potential as a marker of response to treatment and prognosis.

Table 1.2 Common tumour markers.

Tumour marker	Usual reference range	Associated cancers (italics indicate the most relevant)	Associated other conditions	Aid diagnosis	Response assessment	Staging	Prognosis	Monitor for recurrence
AFP (α-fetoprotein)	0–10 ng/mL or 0–12 µg/L	*HCC, germ cell tumours, hepatoblastoma*, hepatobiliary, gastric, lung, colorectal	Pregnancy, hepatitis, cirrhosis, biliary tract obstruction, alcoholic liver disease, ataxia telangiectasia, hereditary tyrosinaemia	X	X			X
β2-microglobulin	< 2.5 mg/L.	*Multiple myeloma, lymphoma*	Many other conditions, including Crohn's disease, hepatitis and renal disease				X	
BTA (bladder tumour antigen)	Urine is either positive or negative	*Bladder*	Renal stones, UTI	X				X
Ca15-3	0–5 to 0–40 U/ml	*Breast*, ovarian, lung	Benign breast conditions, hepatitis, chronic liver disease, colitis, dermatological conditions		X			X
Ca19-9	very variable, from 0–37 U/ml to 0–100 U/ml	*Pancreatic, colorectal, gastric*, hepatocellular, oesophageal, ovarian	Pancreatitis, inflammatory bowel disease, cholangitis, cholestasis, chronic liver disease, diabetes, irritable bowel syndrome, jaundice, cystic fibrosis		X			X

Tumour marker	Usual reference range	Associated cancers (italics indicate the most relevant)	Associated other conditions	Aid diagnosis	Response assessment	Staging	Prognosis	Monitor for recurrence
Ca125	0–35 U/ml	*Ovarian*, breast, cervical, endometrial, hepatocellular, lung, non-Hodgkin's lymphoma, pancreas, peritoneal, uterine, any advanced adenocarcinoma	Endometriosis, menstruation, inflammatory pelvic disease, post-laparoscopy, peritoneal inflammation, non-malignant ascites, hepatitis, chronic liver disease, pancreatitis, respiratory disease (e.g. pneumonia, pleural inflammation), colitis, diverticulitis, irritable bowel syndrome, heart failure, pericarditis, diabetes, ovarian hyperstimulation, pregnancy, recurrent ischaemic strokes, arthritis, sarcoidosis, systemic lupus erythematosus, acute urinary retention, cystic fibrosis		X	X		X
Calcitonin	< 5–12 pg/ml	*Medullary thyroid carcinoma*, lung cancer, leukaemia	Thyroiditis, pernicious anaemia	X	X			X

Continued

Table 1.2 Continued

Tumour marker	Usual reference range	Associated cancers (italics indicate the most relevant)	Associated other conditions	Aid diagnosis	Response assessment	Staging	Prognosis	Monitor for recurrence
CEA (carcinoembryonic antigen)	0–2.5 ng/ml (non-smoker) to 0–5.0 ng/mL (smoker)	*Bowel*, lung, breast, thyroid, pancreatic, liver, cervix, bladder, mesothelioma, oesophageal	Hepatitis, respiratory diseases (e.g. COPD, pneumonia, pleural inflammation), colitis, pancreatitis, higher in cigarette smokers, chronic liver disease (e.g. cirrhosis, chronic active hepatitis), diverticulitis, irritable bowel syndrome, jaundice, renal disease		X			X
Chromogranin A	< 50 ng/mL, results vary by laboratory	*Neuroendocrine tumours*		X	X			
hCG (human chorionic gonadotrophin)	0–5 IU/L	*Testicular, trophoblastic*, lung	Pregnancy, testicular failure, cannabis use, menopause, pituitary adenoma, after termination of pregnancy	X	X			X
LDH (lactate dehydrogenase)	very variable	*Melanoma, lymphoma, testicular cancer, germ cell tumours*	Damage to an organ (e.g. MI)		X	X	X	X

Tumour marker	Usual reference range	Associated cancers (italics indicate the most relevant)	Associated other conditions	Aid diagnosis	Response assessment	Staging	Prognosis	Monitor for recurrence
NSE (neuron-specific enolase)	> 9 ug/mL	*Neuroendocrine tumours*			X			
PSA (prostate specific antigen)	0–4 ng/mL but some advocate age-related reference ranges	*Prostate*	Benign prostatic hypertrophy, ejaculation, prostatitis, increasing age, 5-α reductase inhibitors (e.g. finasteride), catheterisation, digital rectal examination, cystoscopy, prostatic massage/biopsy/USS, acute urinary retention, UTI	X	X			X
Thyroglobulin	Variable depending on assay used	*Thyroid*	Other thyroid diseases					X (and to detect residual disease)

Other relevant sections of this book

Chapter 10, section on personalised medicine

References

American Association for Clinical Chemistry. Tumour markers. Available from: http://www.labtestsonline.org.uk/understanding/analytes/tumor-markers/ (accessed 1 January 2014).

American Cancer Society. Tumour markers 2011. Available from: http://www.cancer.org/Treatment/UnderstandingYourDiagnosis/ExamsandTestDescriptions/TumorMarkers/index (accessed 1 January 2014).

Dawson SJ, Tsui DW, Murtaza M, Biggs H, Rueda OM, Chin SF, *et al*. Analysis of circulating tumor DNA to monitor metastatic breast cancer. *The New England Journal of Medicine*. 2013. 368(13): 1199–209. Epub 13 March 2013.

Duffy M, McGing P. *Guidelines for the Use of Tumour Markers*. Scientific Committee of the Association of Clinical Biochemists in Ireland (ACBI). 2005.

Sleijfer S, Gratama JW, Sieuwerts AM, Kraan J, Martens JW, Foekens JA. Circulating tumour cell detection on its way to routine diagnostic implementation? *European Journal of Cancer*. 2007. 43(18): 2645–50.

Sturgeon CM, Lai LC, Duffy MJ. Serum tumour markers: how to order and interpret them. *British Medical Journal*. 2009. 339:b3527.