Chapter 3
Chemotherapy in the Management of Cancer

Breast Cancer

Breast cancer is now the commonest cancer in Britain. Every year more than 48,000 women, and 300 men, will find they have breast cancer. Overall nearly one in nine women will develop the condition at some time during their lives. The risk of getting the disease increases with age: half of all breast cancers are first diagnosed in women over the age of 65, and a quarter are first diagnosed in women over the age of 75. Breast cancer is getting more common. The number of new cases each year in the UK has doubled over the last 40 years. Although this increase in the frequency of the disease is worrying, it is offset by the fact that the cure rate is rapidly improving. In the early 1990s only about half of all women who had breast cancer could expect to live 10 years or more, but now this figure has increased to more than seven out of ten, and is expected to improve further over the coming years.

Oncologists have debated whether this improvement is due to the introduction of breast screening, with the detection of cancers at an earlier, more curable, stage, or the increasing use of adjuvant chemotherapy. This is a controversial subject but increasingly the evidence is in favour of systemic adjuvant therapy as the major factor in the improving outcome for women with this disease. When considering the use of adjuvant chemotherapy in early breast cancer two key questions are: who should receive treatment, and what

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treatment should they receive? One way to answer these complex issues is to adopt an historical approach.

Following the publication of the results from the early adjuvant studies in the 1970s it was possible, by 1980, to make clear recommendations. In terms of patient selection those women who had axillary node involvement at the time of their initial surgery should be offered systemic adjuvant therapy, whereas this treatment was not necessary for those women whose cancers were node negative. When it came to choosing what drugs to use the evidence suggested that premenopausal women should receive cytotoxic drugs, most frequently with the classical combination of cyclophosphamide, methotrexate and fluorouracil (CMF), and postmenopausal women should be given hormonal therapy, with tamoxifen.

Over the last 25 years it has become apparent that tumour size, receptor status and the histological grade of the cancer, are important prognostic factors, as well as the presence or absence of positive axillary nodes. As a consequence selection criteria have been adjusted to allow for these additional variables. But there is no absolute consensus as to how these criteria should be applied to individual patients. Currently at least three systems are available to make this decision. These are personal experience, prognostic formulae, and a number of on-line tools. Personal experience relies on the judgement of individual specialists, or groups of experts in multidisciplinary teams, making decisions based on their knowledge and judgement. The prognostic formulae take the patient's details, put them into an equation, and produce a number indicating their risk of recurrent disease. The most widely used of these calculations is the Nottingham Prognostic Index, which is as follows:

Nottingham prognostic index

- Tumour size (cm × 0.2) + lymph node stage (1 = node negative, 2 = 1–3 metastatic nodes, 3 = 4+ metastatic nodes;) + histological grade (1 = good, 2 = moderate, 3 = poor).
- A prognostic index <3.4 = good prognosis, 3.4–5.4 = moderately good prognosis, >5.4 = poor prognosis.

Although many clinicians, particularly in the UK, rely on this method it still only produces a score for that patient's risk of

relapse, and there is no universal agreement as to the cut-off level above which systemic therapy is indicated. So, interpreting the answer from the formula, in terms of determining the treatment for a particular patient, is still a matter of personal judgement by the oncologists involved. The on line tools offers an alternative approach. The model for these is 'Adjuvant on line': backed by a database from the National Cancer Institute in the USA this is an internet service, which allows oncologists to enter the details of their patient and then to select a variety of adjuvant treatment options. The programme will then produce probable 5 and 10-year survival figures based on each treatment choice. This allows doctors to see which treatment is likely to be most effective and to get an estimate of the magnitude of the benefit. This system also provides data which are readily understood by patients, and so allows women to enter into a meaningful discussion with their oncologist in making treatment decisions. A number of similar systems have been developed and in 2010 the NHS in the UK introduced its own system 'PREDICT' available at www.nhs.PREDICT.

When it comes to selecting which systemic therapy to use there have been a number of significant changes since the 1980s, including:

- the routine use of oestrogen receptor (ER) testing, and the realisation that only those women with ER+ cancers will benefit from hormone therapy
- the discovery of the aromatase inhibitors as an alternative to tamoxifen for post-menopausal women
- the discovery of a number of new cytotoxic drugs which build on the benefits of the original CMF regime
- the recognition that cytotoxic treatment is beneficial in post-menopausal women, and contributes to increased survival, although at a progressively diminishing level, up to the age of 70 and possibly beyond
- the discovery of HER2 receptors and the recognition that women whose cancers are HER2+ may benefit from the addition of drugs like trastuzumab to their treatment regimen.

The discovery that only those women who had ER+ cancers would benefit from endocrine therapy initially simplified

treatment decisions, but the advent of the aromatase inhibitors has complicated the picture. Clinical trial data suggest that these drugs are marginally more effective than tamoxifen in preventing relapse, reducing the risk of recurrence at 5 years by 3–5%, although their impact on overall survival still remains uncertain. Similar trials have also raised questions about the scheduling of hormonal therapy: traditionally tamoxifen has been given for 5 years but studies have shown that relapse rates can be reduced if either tamoxifen is given for 2–3 years followed by an aromatase inhibitor for 3 years, or tamoxifen is given for 5 years followed by an aromatase inhibitor for a further 3 years. There are also issues around toxicity profile (a greater risk of menopausal symptoms, thromboembolic complications and endometrial hyperplasia and cancer, with tamoxifen, and osteoporosis, with aromatase inhibitors), and cost, with the aromatase inhibitors being significantly more expensive than tamoxifen. At the present time there is no consensus on the optimum way to use endocrine therapy in early breast cancer and decisions will vary from oncologist to oncologist, and patient to patient, but there is a growing feeling that for higher risk patients initial aromatase therapy is probably the treatment of choice whereas for those with less aggressive disease either sequential therapy or tamoxifen alone might be recommended.

Other points to mention in relation to endocrine therapy relate to premenopausal women, and the sequencing of treatment. The aromatase inhibitors only work in postmenopausal women, and although tamoxifen may be used in younger women its effect on ovarian function is variable and unpredictable. In the past when ovarian suppression was considered necessary the choice lay between surgical removal, oophorectomy, or radiotherapy, a radiation menopause. Nowadays, however, these have largely been supplanted by the use of injections of gonaderilin analogues, which offer long-term, but reversible prevention of oestrogen formation. The use of gonaderilin analogues in the adjuvant treatment of young women with breast cancer is variable. Although there are good data from clinical trials suggesting

that they are as effective as cytotoxic drugs they are seldom used as an alternative treatment. However, some oncologists will use them in addition to cytotoxics, particularly in women at high risk of relapse, but the value of this combined therapy has still to be established by clinical trials. In the past when an adjuvant treatment programme combined hormonal and cytotoxic therapy the two modalities were usually given concurrently, but clinical trials have now shown that this reduces the effectiveness of cytotoxic treatment, and the pattern nowadays is to give cytotoxic therapy first, followed by hormonal manipulation. (The theoretical basis for the adverse interaction between endocrine and cytotoxic therapy is that the former reduces the level of cell division in the cancer, putting cells in the resting, G_0, phase of the cell cycle, where they are more resistant to cytotoxic treatment). Incidentally, giving radiotherapy concurrently with cytotoxic treatment does not reduce its effectiveness, although side effects, such as tiredness, may be increased.

When it comes to the choice of cytotoxic drug regimens for adjuvant therapy in early breast cancer there has been a similar evolutionary process. Clinical trials during the 1990s showed that the benefits of classical CMF chemotherapy could be increased by adding an anthracycline drug, usually epirubicin, to the combination. More recently trials have shown that combining epirubicin with a taxane, most often docetaxel, further increases the chance of cure. However, these additional benefits to come at the cost of increased toxicity: for example one major study with the epirubicin-docetaxel combination reported that 25% of women who had the drugs developed neutropenic sepsis. This means that in general oncologists will try to individualise the choice of treatment regimen for their patients, reserving the more aggressive drug combinations for women who are at high risk of relapse, and who are younger and fitter, whilst less intensive schedules are appropriate for older, frailer and lower risk women. Although studies have shown that cytotoxic treatment may have a positive impact on survival in women up to the age of 70, the benefit diminishes steadily over the age

of 50 and so its use in women over 60 is, once again, a matter of weighing up the risks and benefits for individual patients. Over 70 the benefits are less certain, and the risk of significant toxicity increases dramatically, so cytotoxic treatment is less often used and frequently focuses on gentler therapies such as oral capecitabine.

For those women who have HER2+ cancers the addition of trastuzumab to their drug regimen has been shown to further reduce the risk of relapse. However, the extent of this benefit has been exaggerated by the media with an overall reduction of the relapse rate by only a matter of 2% or 3%. There was initial uncertainty over the duration of treatment necessary, but most oncologists are now using a 1 year course of the drug following conventional cytotoxic therapy.

In 2005 those women who had breast cancers which were negative for oestrogen, progesterone and HER2 receptors became defined as having 'triple-negative breast cancer'. Triple-negative cancers typically behave more aggressively than other types of breast cancer but do appear to be more sensitive to cytotoxic therapy. An aggressive approach is usually adopted in adjuvant chemotherapy regimens for these tumours with a typical schedule being cyclophosphamide and epirubicin being followed by a taxane. The platinum drugs, cisplatin and carboplatin, which are not generally used in breast cancer treatment are active in these tumours as is the anti-angiogenic agent bevacizumab and these drugs may play a part in the adjuvant treatment of triple-negative cancers in the future.

When it comes to the treatment of relapsed, metastatic, breast cancer the choice of systemic therapy depends on whether the receptor status of the tumour, and whether there has been previous systemic adjuvant therapy. In the past it has always been assumed that the receptor status of metastases would be the same as the primary cancer but it is now apparent that in about 15% of patients this is not the case and so, if possible, a metastasis should be biopsied to recheck the presence or absence of receptors.

If the cancer is ER+ then hormonal therapy would usually be the first option, unless the disease appears particularly aggressive, when cytotoxics would be preferred. If an

endocrine agent, such as tamoxifen or an aromatase inhibitor, has been given previously as adjuvant therapy, then if the disease-free interval to relapse has been more than a couple of years the same agent could be re-tested, for shorter intervals an alternative drug would usually be chosen.

Once the cancer is no longer be responsive to hormonal manipulation cytotoxics can be introduced. Unless the disease is particularly aggressive the recommendation is for single agent therapy in this situation with drugs such as docetaxel, vinborelbine or capecitabine, the latter being attractive as an oral option. For more aggressive disease then a combination of a taxane with either an anthracycline, gemcitabine or capecitabine are possible combinations, the choice of drugs being influenced in part by what treatment the woman has received previously.

For those women whose cancers are HER2+ there is new evidence that combining trastuzumab with another HER2+ receptor inhibitor, pertuzumab and the cytotoxic docetaxel, may increase the length of remission by 6 months or more compared to the two drug combination.

Suggestions for Further Reading

Amir E, Clemons M, Purdie CA, et al. Tissue confirmation of disease recurrence in breast cancer patients: pooled analysis of multicentre, multi-disciplinary prospective studies. Cancer Treat Rev. 2012:38 in press.

Baselga J, Cortes J, Kim S-B, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012; 366:109–19.

Benson JR, Jatoi I, Keisch M, et al. Early breast cancer. Lancet. 2009;373:1463–79.

Coleman RE, Bertelli G, Beaumont T, et al. UK guidance document: treatment of metastatic breast cancer. Clin Oncol. 2012:24:169–76.

Dowsett M, Cuzick J, Ingle J. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol. 2010;28:509–18.

Early Breast Cancer Trialists Collaborative Group. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analysis of long-term outcome among 100,000 women in 123 randomised trials. Lancet. 2012;379:432–44.

Foulkes WD, Smith IE, Rois-Filho JS. Triple negative breast cancer. N Engl J Med. 2010;363:1938–48.
McPherson K. Screening for breast cancer – balancing the debate. Br Med J. 2010;340:c3106.
Welch HG. Screening mammography – a long run for a short ride. N Engl J Med. 2010;363:1276–78.

Lung Cancer

Lung cancer is the second commonest cancer in Britain. Each year there are more than 35,000 new cases, with some 32,000 people annually dying of the disease. More than 95% of lung cancers are smoking related. Although the incidence in men is decreasing that in women is still rising, giving a current male:female ratio of 3:2. The average age at the time of diagnosis is 65, with less than 2% of people being under the age of 50. Lung cancer can be divided into two main types: small cell lung cancer, which makes up about 20% of cases, and non-small cell lung cancer, which includes adenocarcinomas squamous cell carcinomas, large cell carcinomas and poorly differentiated carcinomas, and accounts for the remaining 80%. The management of these two forms of lung cancer is quite different.

Small Cell Lung Cancer

Small cell lung cancer can be classified as either limited, if the disease is confined to the hemithorax of origin and the mediastinum, or extensive, if there is spread elsewhere; 60–70% of people have extensive disease at the time of diagnosis. Until the 1970s both stages of the disease were uniformly rapidly fatal, with survival times being measured in a matter of weeks to a few months. The advent of intermittent combination cytotoxic chemotherapy dramatically transformed the outlook, as these tumours proved remarkably chemosensitive with about 80% of people going into remission, and about 20% experiencing complete remissions. Unfortunately this good news is offset by two negatives: firstly, most people will relapse, and secondly, when relapse occurs second-line chemotherapy is of limited efficacy.

A wide range of drug combinations have been found to be active as first-line therapy in small cell lung cancer but the combination of etoposide and cisplatin (EC) has emerged as the most successful and is the treatment of choice.

For people with limited stage disease the best results are obtained when EC is given concurrently with radiotherapy to the primary tumour. However, this is quite an intense regimen and for patients who are less fit induction chemotherapy followed by radiotherapy is an option. Overall use of one of these schedules will lead to average survival times of 18–24 months with about 15–20% of people surviving 5 years or more, and possibly being cured. For people with extensive stage disease etoposide combined with either cisplatin or carboplatin is the usual treatment choice and this results in median survival times of 8–13 months.

When good remissions were first seen following chemotherapy in small cell lung cancer one problem was that more than 50% of people relapsed with brain metastases. This was because the drugs used had little or no ability to penetrate the blood brain barrier, so seedlings of tumour that had lodged in the brain were able to continue growing. As a result 'prophylactic' radiotherapy to the brain was introduced for people who went into remission, and this is still usually given today as it reduces the CNS relapse rate by almost 50%.

Although small cell lung cancer is highly chemosensitive initially once people relapse the disease is relatively resistant. Many will be too unwell for active treatment to be considered but for those that are fit enough the main options are either topotecan as a single agent or a combination of cyclophosphamide, doxorubicin and vincristine, which may lead to an increase in survival of 3–6 months.

Non-small Cell Lung Cancer

The cornerstone of treatment for localised disease is surgery, Although this has the potential for cure less than 10% of people are suitable for an operation, either because of the extent of their disease, their general fitness (many people will

have severe respiratory or cardiac problems because of their chronic smoking), or their age. For some of these individuals, radical radiotherapy may be an alternative, but offers a lower chance of cure than surgery.

The following paragraphs describe the role of systemic treatment in non-small-cell lung cancer. This is one of the most rapidly evolving areas of cancer chemotherapy and there have been very significant developments in the last few years and further progress is likely over the next decade. However, a sobering comment on the world of cutting edge new technologies and state of the art clinical trial data was offered by a survey carried out by the Department of Health in the UK in 2010 which showed that only 51% of people with a diagnosis of lung cancer received any form of active treatment (National Lung Cancer Audit, 2010. Department of Health, London).

For many years there was uncertainty as to whether giving adjuvant chemotherapy after apparently successful surgery would improve the outcome, clinical trials over the last decade have given convincing evidence of a benefit. This is, however, dependant on the stage of the cancer: whilst the overall improvement in survival was about 5% following the addition of chemotherapy, in people with stage 1A tumours there was actually a negative effective whilst for those with stage II and III tumours the figure rose to 17%. The treatment was based on either cisplatin and vinorelbine or carboplatin and taxotere, given for four to six courses over 4–6 months. The benefit did not appear to depend on the histology of the cancer. Some studies have also looked at giving chemotherapy prior to surgery (neo-adjuvant treatment). Although this also appears beneficial there is no evidence that it is superior to post-operative treatment.

In people with advanced disease palliative radiotherapy has been the mainstay of treatment for many years. Although this can offer effective symptom control, with cough, dyspnoea, chest pain and haemoptysis being relieved in more than 60% of cases, often by just one or two out-patient treatments, there is no effect on overall survival. In the late 1990s an overview of previous trials showed that platinum-based chemotherapy could increase life-expectancy, albeit by only a modest 6–8 weeks. Since that time further trials have shown

that a variety of regimens can extend median survival times to anywhere from 12 to 24+ months. But patient selection is a key issue. The chance of a benefit is strongly dependant on performance status, with fitter, younger people being the ones most likely to respond; histology and the presence or absence of genetic mutations are also major factors.

For fit patients first-line chemotherapy is based on cisplatin. For those with squamous cell cancers this drug is usually combined with gemcitabine whilst for those with other histologies the doublet is cisplatin/pemetrexed. These combinations can yield median survivals of about 12 months. For less fit patients substituting carboplatin for cisplatin or the use of single agent therapy with either docetaxel, gemcitabine, paclitaxel or vinorelbine are possible treatment options. Some people despite having advanced disease will initially be asymptomatic and it has been suggested that treatment may be delayed in this situation but the evidence from clinical trials is that even in people who are symptom-free the sooner treatment is started the greater the increase in life-expectancy.

Up to 50% of non-small cell lung cancers carry mutations of the epidermal growth factor receptor (EGFR). Positivity for this mutation is more likely in people who have never smoked and those who have adenocarcinomas. Clinical trials have now shown that for those whose cancers carry this mutation the EGFR tyrosine kinase inhibitors erlotinib and gefitinib offer better outcomes than conventional cytotoxic chemotherapy with median survival times in excess of 2 years. As a result routine testing for the presence of EGFR mutation in people being considered for chemotherapy is becoming increasingly widespread.

Another recent development has been the concept of introducing maintenance therapy for those who respond to their initial chemotherapy and there is evidence that in selected patients this may extend survival by a few months.

The improvements in first-line therapy that have been seen in recent years have encouraged increasing exploration of second-line treatment and there is evidence that some patients will benefit from this although the remission durations are usually limited to a few months. The treatment options are summarised in Table 3.1.

Table 3.1 Chemotherapy for advanced or metastatic non-small-cell lung cancer

Clinical scenario	Treatment regimen
First line therapy	
Fit patients (performance status 0–1)	
Squamous cell histology	Cisplatin + gemcitabine
Non-squamous cell histology	Cisplatin + pemetrexed
Adenocarcinoma with +ve EGFR mutation[a]	Gefitinib, erlotinib
Less fit patients (performance status 2)	
	Substitute carboplatin for cisplatin in the above regimens or use single agents (docetaxel, gemcitabine, paclitaxel or vinorelbine)
Maintenance therapy	
Non-squamous cell if did not have pemetrexed initially	Pemetrexed
Adenocarcinoma with +ve EGFR mutation[a]	Gefitinib, erlotinib
Second line therapy	
Non squamous cell	Pemetrexed, gefitinib or erlotinib
Squamous cell	Docetaxel, gefitinib or erlotinib

[a]Some authorities recommend gefitinib and erlotinib for all non-small-cell cancers exhibiting the EGFR mutation

Suggestions for Further Reading

Felip E, Gridelli C, Baas P, et al. Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line and third line therapy. First ESMO consensus conference on lung cancer. Ann Oncol. 2011;22:1507–19.

Goldstraw P, Ball D, Jett JR, et al. Non-small-cell lung cancer. Lancet. 2011;378:1727–40.
NICE clinical guideline 121. Lung cancer: the diagnosis and treatment of lung cancer. NICE. 2011.
Shepherd FA. Maintenance therapy comes of age in non-small-cell lung cancer, but at what cost. J Clin Oncol. 2011;37:4068–70.
Van Meerbeeck JP, Fennell DA, De Ruysscher DKM. Small cell lung cancer. Lancet. 2011;378:1741–55.

Mesothelioma

Mesothelioma is a primary cancer of the pleura (>90% of cases) or peritoneum. It is almost always related to previous asbestos exposure, often 30–40 years previously. There are some 1,700 new cases each year in Britain, with a similar number of deaths. The incidence of mesothelioma is predicted to rise over the next few years to a peak between 2011 and 2015, with the number of cases rising to about 2,000 a year. Mesothelioma is commoner in men than women with a ratio of 6.5:1. The average age at diagnosis is 75. The overall 5 year survival is about 3%, with the median survival being about 9 months.

The very poor outcome for mesothelioma is in part due to the fact that it is usually only diagnosed at an advanced stage. For those few people where the disease is discovered sooner surgery, with an extrapleural pneumonectomy may be an option. For people with more advanced disease cytotoxic chemotherapy combining pemetrexed with cisplatin offers a chance of a response in about 40% of people with a median increase in survival of about 3 months, from 10 to 13 months, and this has become the treatment of choice in this condition.

Suggestions for Further Reading

Rena O. Extrapleural pneumonectomy. Br Med J. 2011;343:d5706.
Tsao A, Wistuba I, Roth J, Kindler HL. Malignant pleural mesothelioma. J Clin Oncol. 2009;27:2081–90.
Vogelzang NJ. Chemotherapy for malignant pleural mesothelioma. Lancet. 2008;371:1640–42.

Urological Cancer

Kidney Cancer

There are 6,000 new cases of kidney cancer each year in Britain, with just over 3,000 people annually dying of the disease. The average age at the time of diagnosis is 60. Renal cancer is twice as common in men than women. Smoking, obesity and hypertension all increase the risk of developing a renal cancer. Clear cell carcinomas account for more than 80% of renal cancers. It has long been recognised that a tiny minority of clear cell carcinomas of the kidney occur as a complication of the rare inherited syndrome von Hippel Lindau disease. The overall 5 year survival figure is 45%. This figure is improving, partly because an increasing number of renal cancers, currently about 30%, are diagnosed as incidental findings in people having abdominal CT scans for some other reason, and hence are discovered at an early, pre-symptomatic, stage.

Surgery, with either a total or partial nephrectomy, is the definitive treatment for renal cancers. Adjuvant chemotherapy has nothing to offer. Historically chemotherapy has had a very limited role in advanced renal cancer: cytotoxics have proved uniformly ineffective. The progestogen hormone Provera has been advocated but responses are rarely, if ever, seen. The cytokines interferon alpha and interleukin have been used but response rates are only of the order of 10%, with no good evidence of increased survival, and both drugs are associated with considerable toxicity.

The appearance of the newer targeted therapies has transformed this depressing picture. There are now a number of drugs which have been shown to have activity in this situation including sunitinib, sorafenib, pazapanib, bevacizumab, temsirolimus and everolimus. The effectiveness of these agents is at least in part explained by angiogenesis inhibition. The background to this is that in von Hippel Lindau disease (VHL) the VHL tumour suppressor gene is inactivated. This same abnormality has now been identified in more than 60% of sporadic clear cell renal carcinomas. VHL inactivation leads to an

increase in levels of vascular endothelial growth factor (VEGF), platelet derived growth factor α (PDGFα), and transforming growth factor a (TDGFa), all of which stimulate new blood vessel formation, and hence support tumour growth. Sunitinib, sorafenib and pazopanib act primarily by inhibiting VEGF and PDGFα receptors whilst the mTOR inhibitors temsirolimus and everolimus acts at a later stage in the pathway by inhibiting signal transduction to the nucleus.

Clinical trials are still establishing the relative merits of these agents in advanced renal cancer but at the present time sunitinib and pazopanib appear the most effective agents offering an increase in survival times of 12 months or more but with so many drugs now available, and the prospect of more in the future, the outlook can only improve in this condition.

Suggestions for Further Reading

NICE technology appraisal guidance 215. Pazopanib for the first-line treatment of advanced renal cell carcinoma. NICE. 2011.

Powles T, Chowdhury S, Jones R, et al. Sunitinib and other targeted therapies for renal cell carcinoma. Br J Cancer. 2011;104:741–5.

Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. Lancet. 2009;373:1119–32.

Schmidinger M, Bellmunt J. Plethora of agents, plethora of targets, plethora of side effects in metastatic renal carcinoma. Cancer Treat Rev. 2010;36:416–24.

Bladder Cancer

Bladder cancer is the fifth commonest cancer in Britain. There are about 14,000 new cases of bladder cancer each year, with 4,700 people annually dying of the disease. The average age at the time of diagnosis is 70. Bladder cancer is three times more common in men than women. Transitional cell carcinomas account for more than 90% of bladder cancers. The overall 5 year survival figure is 65%. This figure hides the fact that bladder cancer is made up of two different types of disease: superficial and invasive cancers.

Superficial bladder cancers are tumours confined to the mucosal lining of the bladder. They make up 70% of bladder cancers. Based on the microscopic appearance of the tumour cells they can be classified as low risk or high risk cancers. Low risk cancers, which account for 60% of superficial tumours, behave in a relatively benign way. High risk cancers carry the risk of transformation to invasive disease. Management of these growths is by an initial cystoscopic resection or diathermy of the cancer, followed immediately by instillation of a chemical into the bladder. The drug is introduced through a catheter at the time of operation, the catheter is then clamped for the next few hours allowing the drug to be partly absorbed by the bladder wall. For low risk tumours all that is then required is a regular follow up cystoscopy to check that there is no evidence of recurrence. For high risk tumours similar regular cystoscopies are offered but are usually followed by further drug instillations. For some patients with extensive high risk disease, where there is considered to be a very strong chance of invasive cancer developing, a radical cystectomy may be offered as an alternative.

The most widely used, and most effective, chemical for bladder instillations is bacille Calmette-Guerin (BCG), which was for many years used as a vaccine against tuberculosis. Quite why it is so effective in treating superficial bladder cancer remains uncertain. Solutions of a number of cytotoxic drugs may be used as an alternative to BCG, among these are mitomycin, epirubicin and doxorubicin.

For invasive cancers surgery is the cornerstone of treatment, with a radical cystectomy being offered. As bladder cancer is mainly a disease of older people many patients will not be fit enough for major surgery and radiotherapy is the treatment of choice for them.

Unfortunately 5 year survival rates are poor: about 35% after surgery, and 25% after radiotherapy. Giving adjuvant chemotherapy after surgery does not significantly improve these figures. However, a number of trials have used a variety of cisplatin-based regimens given pre-operatively (neoadjuvant therapy) and have shown an overall increase in survival of about 5% and this may be offered as a treatment option for fitter patients.

For people with advanced or metastatic bladder cancer the most widely used cytotoxic regimen for many years was M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin). However, this was a toxic regimen and the combination of gemcitabine and cisplatin has now been shown to be as effective with far fewer side effects, and is the treatment of choice. It offers a response rate of about 40% and may increase survival by 4–6 months to a little over 12 months. For older, less fit people, for whom even this combination may be a challenge, single agent therapy with either paclitaxel, gemcitabine or pemetrexed can be given but response rates are only 10–20% and there is little evidence that survival is increased.

Although targeted therapies have been quite extensively explored in the management of advanced bladder cancer none has, as yet, shown significant therapeutic activity.

Suggestions for Further Reading

Gallagher DJ, Milowsky MI, Bajorin DF. Advanced bladder cancer: status of first-line chemotherapy and the search for active agents. Cancer. 2008;113:1284–93.

Kaufman DS, Shipley WU, Feldman AS. Bladder cancer. Lancet. 2009;374:239–49.

Shelley MD, Mason MD, Kynaston H. Intravesical therapy for superficial bladder cancer: a systematic review of trials and meta-analysis. Cancer Treat Rev. 2010;36:195–205.

Prostate Cancer

Prostate cancer is the fourth commonest cancer in Britain, and has recently overtaken lung cancer as the commonest cancer in men. There are more than 32,000 new cases of prostate cancer each year, with some 8,500 men annually dying of the disease. Between 1990 and 2002 the annual age adjusted incidence of prostate cancer nearly doubled in the UK. This was probably largely due to the availability of the prostate specific antigen (PSA) blood test, which allows the condition

to be diagnosed at an early asymptomatic stage rather than a true increase in the frequency of prostate cancer. The average age at the time of diagnosis is 70–75. Increasing age is the greatest risk factor for developing prostate cancer, and it has been estimated that almost 100% of men in their 90s will have the disease. In younger men, in their 50s and 60s the disease tends to behave aggressively whereas in older men, in their 70s and 80s it is often indolent, progressing very slowly, causing few problems and needing little or no treatment. Prostate cancers are adenocarcinomas, and are graded according to their Gleason score, which ranges from 6 to 10, higher scores indicating more aggressive disease and a poorer prognosis. When prostate cancer spreads to other parts of the body it almost invariably goes to the bones. The overall 5-year survival rate is about 70%.

When considering its management prostate cancer can be divided into three stages:

- early disease: when the cancer is confined within the capsule of the prostate gland
- locally advanced disease: when the tumour has breached the capsule and spread into the surrounding tissues or pelvic lymph nodes
- advanced disease: when blood-borne spread to the bones has occurred.

Of those who present with symptomatic disease, as opposed to just a raised PSA level, about 50% of men will have early disease, 25% locally advanced disease, and 25% metastatic disease.

Options for the management of early prostate cancer include radical prostatectomy, radiotherapy (which may be either external beam – conformal or intensity modulated, IMRT, irradiation – or brachytherapy, with the insertion of radioactive seeds into the prostate gland), or policies of watchful waiting or active surveillance. To help decide which treatment is appropriate, men with early prostate cancer can be placed into one of three risk groups according to a number of parameters (Table 3.2).

Table 3.2 Risk stratification of early prostate cancer

	PSA		Gleason score		Clinical stage
Low risk	<10	&	<6	&	T1–T2a
Intermediate risk	10–20	or	7	or	T2b–T2c
High risk	>20	or	8–10	or	T3–T4

For those in the low risk group watchful waiting or active surveillance are usually recommended. Watchful waiting, which is usually more appropriate for older men (with a life expectancy of 10 years or less) who have few symptoms, is intended to delay treatment for as long as possible and to use hormonal therapy as and when therapeutic intervention is needed. Active surveillance is an option for younger men with low risk disease, or some with intermediate risk cancers but few symptoms. In this scenario the aim is to delay treatment for as long as possible but to use an aggressive intervention, with surgery or radiotherapy, as and when treatment is required. For men in the high risk group either surgery or radiotherapy is indicated and for those in the intermediate risk group the choice of treatment is less clear cut and is decided on an individual basis.

A key question is whether giving hormonal therapy in addition to surgery or radiotherapy can improve the outcome. Studies have now shown that there is a definite benefit from combining endocrine therapy with radiation, particularly in men in the high risk group. However, there is no evidence that hormone treatment improves the outcome after prostatectomy. The optimum timing of endocrine treatment (whether started before or after radiotherapy), and its duration (anywhere from 2 months to 2 years) remain to be confirmed. Therapy usually involves either a gonadorelin analogue (such as goserelin, leuprorelin or buserilin), or an anti-androgen (such as bicalutamide, or flutamide).

For locally advanced prostate cancer the options are either external beam radiotherapy (the extent of disease means brachytherapy is not appropriate), or endocrine therapy, or, more usually nowadays, a combination of the two.

Since the mid-1940s endocrine therapy has been the cornerstone of management of advanced prostate cancer. Nowadays the usual first-line approach is medical castration using one of the gonaderilin analogues and this will be effective in controlling the disease for the great majority of men, often for many months or even years. When relapse does occur the disease is termed castration-resistant prostate cancer (C-RPC). It is important to distinguish this from hormone refractory prostate cancer as C-RPC is usually still sensitive to other forms hormone therapy and so second line treatment with an anti-androgen, such a bicalutamide, flutamide or cyproterone, will often gain a further remission. Third and fourth line hormonal therapies are dexamethasone and stilboestrol. The place of the new inhibitor of androgen synthesis, abiraterone, has still to be established. One aspect of endocrine therapy in this context which remains controversial is total androgen blockade: this involves giving an anti-androgen along with a gonaderlin analogue as first-line treatment. Trials have shown that combining the two approaches to androgen inhibition does improve 5 year survival by about 5% but this benefit is relatively small and obtained at a cost of extra morbidity and expense which many oncologists feel is not justified by the modest improvement in outcome.

Traditionally hormone therapy has been given continuously for men with metastatic prostate cancer but recently it has been suggested that treatment might be equally, or even more, effective, if given on an intermittent basis. Clinical trials using various schedules have indicated that this might be the case, and even if there is no actual survival advantage then the time off-treatment has benefits in terms of quality of life for patients and the overall cost of treatment, so this approach is increasingly entering into routine practice.

Once the cancer does become hormone refractory cytotoxic treatment can be considered. Until a few years ago it was widely agreed that cytotoxic therapy played little or no part in the treatment of advanced prostate cancer. But in 2005 studies were published showing that giving docetaxel combined with prednisolone could actually lead to a median increase in survival of about 3 months. Although this is a modest benefit there is also evidence that giving cytotoxic

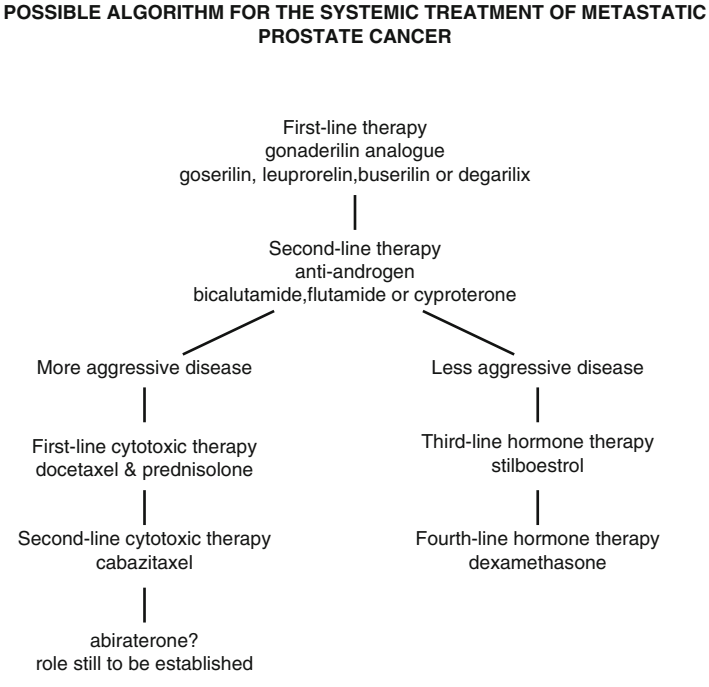

Figure 3.1 Possible algorithm for the systemic treatment of metastatic prostate cancer

therapy with docetaxel may help with symptom control and improve quality of life for many men. Recent trials have shown that on relapse the new cytotoxic cabazitaxel or the immunomodulator sipuleucel-T can offer a further increase in survival of a few months but at the present time the limited data on these compounds and their considerable cost are limiting their availability. These systemic therapeutic options are summarised in Fig. 3.1.

Finally for most men with bone metastases, who will make up the vast majority of this population, either a bisphosphonate or denosumab would usually form part of the treatment regimen, to help with control of pain and reduce the risk of one complications (see page 38).

Suggestions for Further Reading

Collins R, Trowman R, Norman G, et al. A systematic review of the effectiveness of docetaxel and mitoxantrone for the treatment of metastatic hormone-refractory prostate cancer. Br J Cancer. 2006; 95:457–62.

De Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364:1995–2005.

De Bono JS, Oudard S, Ozgroglo M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment. Lancet. 2010;3761:1147–54.

Kantoff PW, Higano CS, Shone ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363: 411–22.

Mottet M, Bellmont J, Bolla M, et al. EUA guidelines on prostate cancer: part II: treatment of advanced, relapsing and castration-resistant prostate cancer. Eur Urol. 2011;59:572–83.

Testicular Cancer

There are just over 2,000 new cases of testicular cancer each year in Britain. Although this is a relatively small number it is the commonest form of cancer in men under 45, with an average of onset of 30. The incidence of testicular cancer has doubled in the last 40 years, and is still rising at 3–6% per annum. The reason for this increase is unknown. Germ-cell tumours make up more than 95% of testicular cancers and are made up of seminomas (55% of all cases) or non-seminomatous cancers. The latter is a heterogenous group comprising teratomas, embryonal carcinomas, yolk sac tumours and choriocarcinomas but the cancers are usually a mix of these histologies, often with a seminoma component as well, rather than being pure tumour types. Surgery, with removal of the affected testis is the first line of treatment. Testicular cancer has been a major success story for cytotoxic chemotherapy, 50 years ago metastatic disease was universally fatal, today, even for men with poor prognosis secondary disease, two out three can expect to be cured, and the overall cure rate for testicular cancer is in excess of 95%.

In the past radiotherapy to the para-aortic and ipsilateral iliac lymph nodes was offered as standard adjuvant therapy for men with early stage seminomas. Latterly trials have shown that low dose radiotherapy confined to the para-aortic nodes is adequate, and causes less long-term morbidity. Recently trials have also shown that a single course of the cytotoxic carboplatin is equivalent to irradiation. So currently the options for management are surveillance only, para-aortic radiotherapy or carboplatin. If the disease has spread to the iliac or para-aortic the irradiation plus carboplatin is recommended. For metastatic disease three courses of BEP cytotoxic chemotherapy (see below) is the standard of care.

The management of non-seminomatous cancers was transformed by the introduction of the BEP regimen in the 1970s. This comprises the three drugs bleomycin, etoposide and cisplatin. After an orchidectomy to remove the primary cancer 25–30% of men with early stage disease will relapse. Options for management after orchidectomy are close surveillance, with regular scans and measurements of tumour markers, offering treatment only when relapse is apparent, or a para-aortic lymph node dissection plus chemotherapy, or two courses of BEP chemotherapy. The choice is determined in part by the histological pattern of the tumour. For men who have metastatic disease the definitive treatment is four courses of BEP.

As present outcomes are so good the main focus for future development is the search for less toxic treatment regimens which will minimise the risk of long-term side-effects.

Suggestions for Further Reading

Feldman DR, Bosl GJ, Sheinfeld J, Motzer RJ. Medical treatment of advanced testicular cancer. JAMA. 2008;299:672–84.

Horwich A, et al. Testicular germ-cell cancer. Lancet. 2006;367:754–65.

Howard GCW, Nairn M. Management of adult testicular germ cell tumours: summary of updated SIGN guidance. Br Med J. 2011; 342:d2005.

Pliarchopoulou K, Pectasides D. First-line chemotherapy of non-seminomatous germ cell tumours (NSGCTs). Cancer Treat Rev. 2009;35:563–9.

Gastrointestinal Cancer

Oesophageal Cancer

Oesophageal cancer is the ninth commonest cancer in Britain. There are about 7,500 new cases of oesophageal cancer each year, with some 6,500 people dying annually of the disease. The average age at the time of diagnosis is 72. Cancers of the upper and middle third of the oesophagus are usually squamous carcinomas whereas those of the lower third are adenocarcinomas. Squamous cancers used to be the more common of the two, but in recent years the incidence of adenocarcinomas has been increasing and these now account for half of all oesophageal cancers. Overall cancer of the oesophagus is about twice as common in men than women, but adenocarcinomas are five times more common in men. The overall 5 year survival figure in the UK is 8%.

For people with localised squamous carcinomas of the upper third of the oesophagus chemoradiotherapy has largely taken over from surgery as the treatment of choice. The most widely used drug regimen in this situation is a combination of cisplatin and fluorouracil. For localised squamous carcinomas of the middle and lower third either chemoradiotherapy alone or chemoradiotherapy followed by surgery are treatment options, the latter probably offering an increased chance of cure but demanding a high level of fitness in potential patients. For localised adenocarcinomas of the middle and lower third of the oesophagus pre-operative (neoadjuvant) chemotherapy with cisplatin and fluorouracil is recommended. For adenocarcinomas of the gastro-oesophageal junction peri-operative chemotherapy is the optimum approach, giving epirubicin and cisplatin with either fluorouracil or capecitabine both prior to, and for a number of weeks after, surgery.

For patients with advanced disease chemotherapy has been shown to increase survival. There is no consensus on the optimum regimen but for both squamous and adenocarcinomas epirubicin, cisplatin and fluorouracil, or epirubicin and oxaliplatin with either fluorouracil or capecitabine are options

and offer median survivals of about 9–10 months. For those with gastro-oesophageal adenocarcinomas which are positive for over-expression of HER2 receptors adding trastuzumab to cytotoxic treatment increases median survival by a further 2–3 months.

Despite the encouraging improvements in outcome with the greater use of chemotherapy in recent years it must be remembered that many of these figures come from clinical trials, which have included younger fitter patients. Unfortunately many people with oesophageal cancer are still too old and frail when their diagnosis is made to allow anything more than good supportive care, to maximise their quality of life in their terminal illness.

Suggestions for Further Reading

Allum WH, Blazeby J, Griffin SM, et al. Guidelines for the management of oesophageal and gastric cancer. Gut. 2011;60:1449–72.

Mariette C, Piessen G, Briez N, et al. Oesophagogastric junction adenocarcinomas: which therapeutic approach? Lancet Oncol. 2011;12:296–305.

Stomach Cancer

There are about 8,500 new cases of stomach cancer each year in Britain, making it the seventh commonest cancer. Unlike many other cancers, the overall incidence of gastric cancer is decreasing, the numbers in the UK having halved over the last 30 years. However, cancers affecting the proximal part of the stomach, the cardia, are increasing in frequency and now comprise the commonest form of stomach cancer. Some 5,500 people die annually of the disease. The average age at the time of diagnosis is in the early 60s. Cancer of the stomach is commoner in men than women with a ratio of 5:3. The overall 5 year survival figure in the UK is 15%.

Surgery is the cornerstone of treatment for gastric cancer but unfortunately only a minority of patients have operable disease at the time of their presentation. Studies of post-operative adjuvant chemotherapy have been done over the last 25 years

but there is no convincing evidence of a benefit. However, trials using peri-operative chemotherapy, giving cytotoxic treatment both before and after surgery, have shown modest improvements in survival and this has now become the standard of care for people with operable gastric cancer in Britain and Europe, with epirubicin and cisplatin combined with either fluorouracil or capecitabine being the treatments of choice. In the United States postoperative adjuvant therapy with chemoradiation, using fluorouracil and leucovorin as the cytotoxic treatment is a more popular approach.

In advanced disease the cisplatin, epirubicin and fluorouracil or capecitabine regimens have been the most widely used and produce responses in up to 60% of patients with an increase in survival of 4–6 months. About 20% of gastric cancers overexpress HER2 receptors and studies have looked at adding trastuzumab to cytotoxic chemotherapy for these patients and have reported modest improvements in overall survival of about 2 months on average.

Suggestions for Further Reading

Allum WH, Blazeby J, Griffin SM, et al. Guidelines for the management of oesophageal and gastric cancer. Gut. 2011;60:1449–72.

Hartgrink HH, Jansen EPM, van Grieken NCT, van de Velde CJH. Gastric cancer. Lancet. 2009;374:477–90.

Okines AFC, Cunningham D. Trastuzumab in advanced gastric cancer. Eur J Cancer. 2010;46:1949–59.

Carcinoma of the Pancreas

There are about 7,000 new cases of pancreatic cancer each year in Britain, making it the tenth commonest cancer. About 6,400 people die annually from the disease. The average age at the time of diagnosis is in the early 70s. Cancer of the pancreas is equally common in both sexes. The overall 5 year survival figure in the UK is 2% and most people survive less than 6 months.

Surgical resection offers the only hope of cure but less than one in ten patients will have operable disease and even

then the 5 years survival rate is only of the order of 10%. Clinical trials have looked at both adjuvant chemotherapy and adjuvant chemoradiation to try and improve these figures. The chemotherapy regimens have been based on fluorouracil or gemcitabine. Adjuvant chemotherapy seems to be of some value, possibly increasing 5 year survival from about 10% to about 20%, but chemoradiation remains controversial with trial results being variable: it is not widely used in Europe but is often given in the USA.

Many people with advanced pancreatic cancer will be too ill, and will deteriorate too rapidly, for chemotherapy to be considered. For those patients who are considered for treatment gemcitabine is the most active single agent. Over the last decade clinical trials have explored combining gemcitabine with a number of other cytotoxics including fluorouracil, capecitabine, cisplatin, oxaliplatin or irinotecan. Meta-analyses suggest that combining gemcitabine with a platinum drug or a fluoropyrimidine (fluorouracil or capecitabine) does increase median survival and one recent study has shown that a triple drug regimen of fluorouracil, irinotecan and oxaliplatin gave a median survival of almost 11 months compared to 6 months with gemcitabine.

Suggestions for Further Reading

Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817–25.

Pliarchopoulu K, Pectasides D. Pancreatic cancer: current and future treatment strategies. Cancer Treat Rev. 2009;35:431–6.

Vincent A, Herman J, Schulick R, et al. Pancreatic cancer. Lancet. 2011;378:607–20.

Colorectal Cancer

Colorectal cancer is the third commonest cancer in Britain. There are more than 34,000 new cases of colorectal cancer each year, with 17,000 people annually dying of the disease. There

are about 22,000 new case of colon cancer and about 12,000 of rectal cancer each year. The average age at the time of diagnosis is 70. Colon cancer is equally common in men and women but rectal cancer occurs more often in men with a male:female ratio of 3:2. Most colorectal cancers are thought to arise from pre-existing polyps in the wall of the bowel and about 5% are due to the inherited conditions familial polyposis coli or hereditary non-polyposis coli (these account for most of the cases in younger age groups). Wherever possible, surgery is the cornerstone of treatment. The overall 5 year survival figure in the UK for both colonic and rectal cancer is 50%.

In the 1950s fluorouracil was identified as the only cytotoxic drug to have any significant activity in colorectal cancer, but even so response rates were disappointing with only about one in ten people with advanced disease seeing a benefit. In the 1970s the addition of folinic acid (leucovorin), which prolongs the inhibition of fluorouracil's target enzyme, thymidylate synthase, brought about an improvement with response rates in metastatic disease rising to about 30%. Over the next decade a lot of work went into exploring different schedules of administration of the two drugs to maximise their efficacy. Regimens which evolved included low dose folinic acid and bolus injections of fluorouracil (Mayo), high dose folinic acid, bolus and infusion of fluorouracil (de Gramont) and prolonged intravenous infusion of fluorouracil (Lokich). During this time clinical trials also showed that the drugs had some activity as adjuvant therapy in earlier stages of the disease. In the mid 1990s three further active cytotoxics were introduced: irinotecan, oxaliplatin and the oral drug capecitabine, which is similar to fluorouracil in its mode of action. More recently a number of monoclonal antibodies have also shown some promise in the treatment of bowel cancer, these include the anti-angiogenic agent bevacizumab and the EGFR inhibitors cetuximab and panitumumab. With so many recent developments the role of chemotherapy in colorectal cancer is still evolving, and the optimum management is for patients to go into clinical trials whenever possible.

In stage III colon cancer, when the disease has reached local lymph nodes but there is no obvious distant spread,

adjuvant chemotherapy is generally recommended for patients under the age of 70 (although often given, the value of adjuvant chemotherapy in people over 70 is uncertain and controversial with some major studies showing no increase in survival but an increase in treatment-related morbidity). With fluorouracil, leucovorin-based regimens an increase in 5 year survival of about 10% can be expected. Newer regimens adding oxaliplatin or the combination of oxaliplatin and capecitabine to these drugs, suggest this figure may be increase by a further 4% in patients under the age of 70.

For people with stage II colon cancer the benefit of adjuvant chemotherapy is less certain, with perhaps a 3–5% improvement in 5 year survival, and guidelines suggest it should be reserved for those people who are considered to be at high risk of recurrence. But some oncologists do question the value of this treatment, pointing out that of every 100 patients given adjuvant chemotherapy only between 3 and 5 will benefit: about 70% will have been cured by surgery and a further 25% will relapse despite having adjuvant drug treatment.

Incidentally, the 'Adjuvant on line' service (see page 107) is also programmed for colorectal cancer, to help clinicians, and patients decide on the whether treatment is appropriate, and which agents should be given.

In stage II and III rectal cancer the focus has been on combining chemotherapy and radiation. Post-operative chemoradiation, using fluorouracil and leucovorin, has been shown to reduce local recurrence rates and improve long-term survival. With the introduction of routine MRI scanning to accurately stage tumours pre-operatively it has been possible to clearly identify those cancers which are locally advanced and for these pre-operative chemoradiation is increasingly being offered. This neo-adjuvant therapy can lead to a complete response rate of about 20%, with no trace of the tumour being detectable at surgery. The initial trials looking at this approach to treatment used infusions of fluorouracil concurrently with radiotherapy and the hope had been that using newer agents like oxaliplatin or capecitabine might improve

on these results but so far, disappointingly, this has failed to be the case, with the newer drugs increasing toxicity without increasing benefit. Incidentally, toxicity is often considerable with the combination of radiation and chemotherapy and this is s treatment that is only suitable for younger, fitter people.

In metastatic colorectal cancer the optimum management has still to be defined. Most bowel cancers spread to the liver, and when the disease is localised within the liver surgical resection of metastases may result in a cure. The criteria for considering surgery are widening all the time but at present about 15% of people with liver secondaries are eligible for surgery and of these about 30–35% will survive 5 years or more. Increasingly chemotherapy is being used pre-operatively to shrink the size and number of liver secondaries which further increases the number of people for whom resection is possible, and improves the outcome.

For people with metastatic disease for whom there is no possibility of hepatic resection survival averages 9–10 months. Giving fluorouracil-leucovorin chemotherapy increases this to an average of 12 months. Early studies adding oxaliplatin (the FOLFOX regimen) showed life expectancy extended to a median of about 15 months but later studies, using modified drug does and scheduling are reporting average survivals of 20 months or more. The use of irinotecan with fluorouracil (FOLFIRI) or capecitabine can give similar results. Adding targeted therapy, with one of the monoclonal antibodies, has the potential for further benefit.

The EGFR inhibitors cetuximab and panitumumab are only effective in people whose cancers do not have a specific KRAS mutation (these wild type KRAS tumours account for about 60% of colon cancers, so the majority of patients will be eligible for treatment), whereas the anti-angiogenic agent bevacizumab is not dependant on specific gene profiles. Adding cetuximab to the combination of fluorouracil or capecitabine and irinotecan increases overall survival in metastatic disease by about 3 months, although combining cetuximab with oxaliplatin and fluorouracil appears less effective. Adding bevacizumab to either oxaliplatin or irinotecan and fluorouracil or

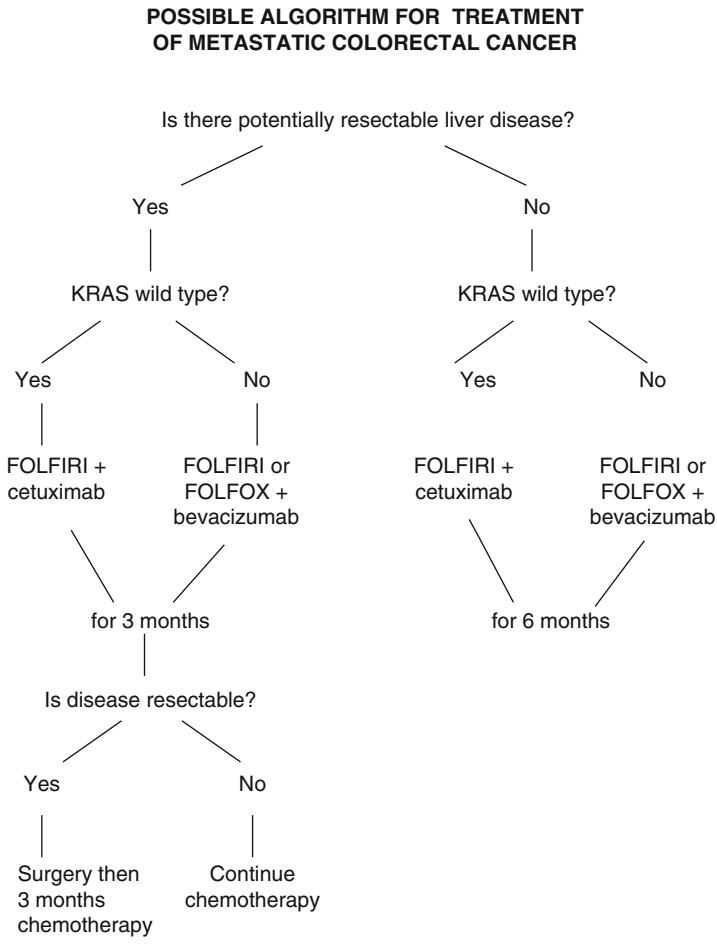

FIGURE 3.2 Possible algorithm for treatment of metastatic colorectal cancer

capecitabine gives a similar survival benefit (although in England at the present time NICE has not approved bevacizumab in this indication on cost grounds). These systemic therapeutic options are summarised in Fig. 3.2.

Suggestions for Further Reading

Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatments in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27:3109–16.

Cunningham D, Atkin W, Lenz H-J, et al. Colorectal cancer. Lancet. 2010;375:1030–47.

Grothey A. Adjuvant chemotherapy in colon cancer – is it worth it ? Eur J Cancer. 2010;46:1768–9.

Haller DG, Tabemero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011;29:1465–71.

Hewish M, Cunnigham D. First-line treatment of advanced colorectal cancer. Lancet. 2011;377:2060–2.

Primrose JN. Surgery for colorectal liver metastases. Br J Cancer. 2010;102:1313–8.

Weiser M. Rectal cancer trials: no movement. J Clin Oncol. 2011; 29:2746–8.

Gynecological Cancer

Cancer of the Ovary

There are about 7,000 new cases of ovarian cancer each year in Britain, with nearly 4,500 women dying annually of the disease. It is the fourth commonest cancer in women. The average age at the time of diagnosis is 70. There are many different histological types of cancer of the ovary but the great majority are adenocarcinomas, arising from the serosal surface of the organ; this summary focuses on these tumours. The overall 5 year survival figure in the UK is about 35%.

The first line of treatment for ovarian cancer is surgery, with removal of both ovaries, the fallopian tubes and uterus. Even when the growth has spread into the peritoneal cavity surgery is still recommended, with as much of the metastatic disease as possible being removed (debulking surgery). For those women with very early disease, where the tumour is well differentiated and confined to one ovary, no further

treatment is indicated but for all others the standard of care is adjuvant cytotoxic chemotherapy. For women with poorly differentiated cancer confined to one ovary this may be carboplatin as a single agent but for all others it should be six courses of a platinum and taxane based combination.

Another approach to post-surgical chemotherapy is the addition of intraperitoneal drug administration, via a catheter through the abdominal wall, into the peritoneal cavity. A number of regimens have been used. One of the most recent, and most successful, involved giving conventional courses of intravenous cisplatin and paclitaxel, followed by intraperitoneal cisplatin 2 and 8 days later. Whilst this did lead to a prolongation of overall survival, compared to intravenous chemotherapy alone, it did cause a considerable increase in toxicity. At present intraperitoneal chemotherapy remains an essentially experimental treatment for ovarian cancer.

Ovarian cancer is chemosensitive and even with advanced disease about 75% of women will gain a remission. However, after about 18–24 months most will relapse with recurrent disease. At this stage treatment depends on their response to first-line chemotherapy, which falls into four categories:

- platinum-sensitive disease: this is a cancer that responds to first-line platinum based chemotherapy and relapses more than 12 months after completion of that therapy.
- partially platinum-sensitive disease: this is a cancer that initially responds to platinum based chemotherapy but relapses between 6 and 12 months after treatment has been completed.
- platinum-resistant disease; this is where the cancer responds initially but relapses within 6 months of completing platinum based chemotherapy.
- platinum-refractory disease: this where the cancer does not respond at all to platinum based chemotherapy.

For women with platinum-sensitive, or partially platinum-sensitive, disease then a further trial of either cisplatin or carboplatin, combined with paclitaxel, is recommended. For women with platinum-resistant, or platinum-refractory, disease single agent paclitaxel can be tried.

An alternative second-line (or subsequent) treatment for partially platinum-sensitive, platinum-resistant or platinum-refractory disease is the liposomal form of doxorubicin: pegylated liposomal doxorubicin. Another option for the latter two groups is single agent topotecan therapy.

Investigation of the newer targeted therapies has focused on bevacizumab and recent clinical trials have shown that when added to conventional carboplatin/paclitaxel-based cytotoxic chemotherapy for women with advanced ovarian cancer disease-free survival is increased by an average of 2–4 months. To what extent this will translate into an increase in overall survival is uncertain at present and cost considerations may also restrict the use of this approach to treatment.

Suggestions for Further Reading

Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365:2473–83.

Hennessy BT, Coleman RL, Markman M. Ovarian cancer. Lancet. 2009;374:1371–82.

Krasner C, Duska L. Management of women with newly diagnosed ovarian cancer. Semin Oncol. 2009;36:91–105.

Martin LP, Schilder RJ. Management of recurrent ovarian carcinoma: current status and future directions. Semin Oncol. 2009;36:112–25.

Perrren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011;365:2482–96.

Redman C, Duffy S, Bornham N, et al. Recognition and initial management of ovarian cancer: summary of NICE guidance. Br Med J. 2011;342:d2073.

Cervical Cancer

There are about 3,100 new cases of invasive cervical cancer each year in Britain, with 1,200 women dying annually of the disease. It is the seventh commonest cancer in women. The disease can appear any time after the age of 20 and there are

two peaks of incidence at about 40 and in the early 70s. Seventy percent of cervical cancers are squamous carcinomas, 15% are adenocarcinomas and the remainder are mixed tumours. The overall 5 year survival figure in the UK is about 65%.

The treatment of invasive cervical cancer is stage-dependant. For early disease (stages Ib to IIa) radical surgery and radical radiotherapy are equally effective, leading to a cure for about 90% of women. For locally advanced disease (stages IIb to IVa) chemoradiation is generally the preferred treatment. The most successful drug in this context has been cisplatin, and a number of clinical trials have shown that combining it with radiation increases survival from about 60% to 80%, when compared with radiotherapy alone. To try and improve on these figures newer trials are looking at combining other cytotoxics with cisplatin, candidate drugs include paclitaxel and gemcitabine. The success of chemoradiation in bulky cervical cancer has led some clinicians to use it in earlier stage disease, either as an alternative or and adjunct to surgery.

For recurrent or advanced cervical cancer cisplatin has shown activity when used as a single agent, giving response rates of about 20%. When combined with paclitaxel this figure rises to about 35%, with median survival times of about 12 months. Other cytotoxic drugs that have shown activity in cervical cancer are gemcitabine, vinorelbine and topotecan but when combined with cisplatin none of these is superior to the combination of paclitaxel with cisplatin. Recently phase II studies have shown that bevacizumab has some activity in this disease and further trials are underway to clarify whether there is a role for this drug in cervical cancer.

Although they do not fall strictly under the heading of chemotherapy, it is important to mention that two vaccines are now available to protect against cervical cancer. More than 95% of cervical cancers are linked to human papilloma virus (HPV) infection, and about 70% are specifically linked to the type 16 and 18 HPV virus. Two vaccines, Gardasil and Cervarix have been developed against HPV 16 and 18 and their recent

availability, and the introduction of mass vaccination programmes, offer the possibility of a dramatic reduction in cervical cancer incidence over the coming decades.

Suggestions for Further Reading

GSK Vaccine HPV-007 Study Group. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18AS04-adjuvaned vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. Lancet. 2009;374:1975–85.

Monk BJ, Sill MW, Burger RA, et al. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix. J Clin Oncol. 2009;27:1069–74.

Monk BJ, Sill MW, McMeekin DS ,et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2009;27:4649–55.

Munoz N, Manalastas R, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomised, double-blind trial. Lancet. 2009;373:1949–57.

Pectasides D, Kamposioras G, Papaxoinis G, Pectasides E. Chemotherapy for recurrent cervical cancer. Cancer Treat Rev. 2008;34:603–13.

Tewari KS, Monk BJ. Recent achievements and future developments in advanced and recurrent cervical cancer. Semin Oncol. 2009; 36:170–80.

Uterine Cancer

There are about 4,500 new cases of cancer of the womb each year in Britain, with 900 women dying annually of the disease. It is the fifth commonest cancer in women. The disease is rare before the age of 40 but rises rapidly in incidence between 40 and 50 remaining relatively constant thereafter until the age of 80, when its frequency declines. More than 85% of uterine cancers are adenocarcinomas arising from the endometrial lining of the organ. The remainder are either squamous cell carcinomas or uterine sarcomas. Between 70% and 80% of endometrial adenocarcinomas will be positive

for progesterone receptors (PgR+), these are more likely to be present in well-differentiated tumours. The overall 5 year survival figure in the UK is about 76%.

The first line treatment for endometrial adenocarcinomas is surgery, which will usually involve a hysterectomy and bilateral salpingo-oophorectomy. More than 80% of these will be early, stage I or II lesions and there is no place for adjuvant therapy in these tumours. For stage III endometrial cancer radiotherapy has traditionally been the adjuvant therapy of choice but at least one clinical trial has suggested that chemotherapy, with the combination of cisplatin and doxorubicin may give better results and this has led to studies exploring the possibility of combining radiotherapy and chemotherapy to maximise the benefit. These trials are still in progress so the optimum adjuvant therapy for more advanced endometrial cancer remains to be established.

For women with metastatic or relapsed disease hormonal treatment with progestogens, such as medroxyprogesterone acetate or megestrol acetate, is often worthwhile and can lead to quite long-lasting remissions. For hormone resistant cancers cytotoxic therapy is an option. Studies have shown that the combination of cisplatin, doxorubicin and paclitaxel can produce responses in more than 50% of women and increase survival to around 15 months, compared to 8 or 9 months with single agent therapy. However, the triple drug regimen is quite toxic, and so using gentler single agent therapy with a platinum drug, taxane or anthracycline may still be preferable in some cases, especially as one is often dealing with an older population with significant comorbidities.

Suggestion for Further Reading

Carey MS, Gawlik, C, Fung-Kee M, et al. Systematic overview of systemic therapy for advanced or recurrent endometrial cancer. Gynecol Oncol. 2006;101:158–67.

Moxley KM, McMeekin. Endometrial cancer: a review of chemotherapy, drug resistance, and the search for new agents. Oncologist. 2010;15:1026–33.

Ray M, Fleming G. Management of advanced-stage and recurrent endometrial cancer. Semin Oncol. 2009;36:145–54.

Brain Tumours

Primary brain tumours make up about 1% of all cancers. They are a very diverse group of malignancies. Numerically the gliomas dominate (these are tumours arising from the supportive tissues within the brain, rather than neural tissue). Of the gliomas by far the most common are the astrocytomas, with nearly 4,000 new cases in adults each year in Britain, and about 3,000 deaths each year. Astrocytomas are also the commonest of all solid tumours in children. In adults the incidence of astrocytomas increases progressively with age, the average age at diagnosis being about 57. Astrocytomas are classified according to their histological appearance into either low grade (Grades I and II) or high grade (Grades III and IV) lesions. Grade III lesions are also known as anaplastic astrocytomas and grade IV astrocytomas are also known as glioblastoma multiforme. Low grade astrocytomas behave in a relatively benign fashion, and chemotherapy plays little or no part in their management, with surgery or radiotherapy being the definitive treatments. High grade astrocytomas, which account for more than 60% of these tumours, behave much more aggressively and carry a poor prognosis. Age is a strong predictor of outcome for high grade tumours, with about 50% of those under 40 surviving 18 months or more, whereas for people over 60 the figure is less than 10%. The overall 5 year survival is less than 5%.

With their aggressive behaviour and frequent rapid deterioration, many people with high grade astrocytomas, especially the elderly and those with a poor performance status, are not candidates for active treatment.

Many patients get dramatic short-term symptomatic relief from high-dose steroid therapy (dexamethasone, up to 16 mg daily), and for many people this, combined with general supportive care is the most appropriate treatment. For younger fitter patients surgery is often considered, but even when performed it is usually only possible to debulk the tumour rather than remove it completely. In this situation implantation of

Gliadel wafers at the time of operation may improve the outcome. These Gliadel implants are disc-shaped gel wafers, about 1 cm across. They contain the cytotoxic carmustine, and slowly dissolve in the brain, releasing the drug into the surrounding tissues over a period of 2–3 weeks.

For most people who have surgery this will be followed by radiotherapy to the brain, and radiotherapy is also the treatment option for those patients who were not suitable for surgery but are still fit enough for active treatment to be considered. Studies have suggested that adjuvant chemotherapy may be of value in selected patients, increasing survival by 2–3 months, and the two regimes that have been most widely used in the past are lomustine (CCNU), as a single agent, and PCV (procarbazine, lomustine and vincrtistine). These have now been widely superceded by temozolamide. When this drug is given during radiotherapy and for up to 6 months thereafter average survival times are increased by about 6 months, when compared to radiation alone. A completely different approach to adjuvant therapy that has been suggested is the use of chloroquine. This drug, usually used to treat malaria, augments the oxidative stress in glial cells caused by radiotherapy and thus enhances the effect of irradiation.

For people who relapse or have progressive disease, and have not had it before, temozolamide, is becoming the drug of choice, supplanting lomustine and PCV although these treatments remain options for those who have previously received temozolamide or who are no longer responding to it.

Suggestions for Further Reading

Munshi A. Chloroquine in glioblastoma – new horizons for an old drug. Cancer. 2009;115:2380–3.

Stupp R, Tonn J-C, Brada M, Pentheroudakis G. High grade malignant glioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v190–3.

Wen PY, Kesari S. Malignant gliomas in adults. N Engl J Med. 2008;359:492–507.

Head and Neck Cancer

In Britain there are nearly 9,000 new cases of head and neck cancer each year, with some 2,700 deaths. Head and neck cancers comprise a very diverse group of tumours, but more than 80% are squamous cell carcinomas of the oral cavity, oropharynx or larynx. This discussion will be restricted to these lesions. They occur more often in men than women, at a ratio of 2.5:1. The average age at diagnosis is around 65. The overall 5 year survival rate for squamous cell cancers of the oral cavity and oropharynx is about 47%, whilst that for laryngeal cancers is about 65%.

Head and neck cancer is one area in oncology where the role of chemotherapy is developing particularly rapidly. This constantly evolving situation means that there are no universally agreed guidelines and practice is likely to vary quite significantly from centre to centre. As far as first line treatment is concerned either surgery or radiotherapy maybe appropriate depending on factors such as the site and size of the tumour and the general fitness of the patient.

In recent years clear evidence has emerged that the results of radiotherapy can be improved by giving concurrent chemotherapy (chemoradiation), particularly in people with locally advanced disease. Overall giving cytotoxic treatment alongside radiotherapy appears to increase the chance of cure by about 6%. This does, however, increase the risk of severe side-effects and so is generally avoided for those with very early stage disease (where less intensive treatment is still effective), or those who are less fit or who have metastatic disease. Cisplatin is the most widely used cytotoxic in combination with radiation. However, trial data has also shown that combining the EGFR antagonist cetuximab with radiotherapy also increases survival, compared to radiotherapy alone, without a significant increase in toxicity. As yet there are no data comparing chemoradiation with cisplatin with chemoradiation with cetuximab, but the latter does appear to offer a less toxic regimen for less fit patients. These results also offer the possibility of exploring the effect of combining cetuximab with cisplatin-based chemoradiation.

Giving conventional adjuvant cytotoxic chemotherapy after surgery or radiotherapy has not been shown to clearly improve long-term survival. However, the observation that when patients relapse after chemoradiation it is usually because of distant metastases, rather than local recurrence of the disease, has led to the suggestion that induction, or neo-adjuvant, chemotherapy, given prior to the chemoradiation might improve the long-term results. Clinical trials using combinations of either paclitaxel or docetaxel with cisplatin and fluorouracil as induction therapies have shown promising results. For patients with locally advanced, bulky disease, neo-adjuvant therapy may also act as a good predictor of response to radiotherapy, with patients achieving a good partial response being likely to benefit from intensive chemoradiation whereas those who show no obvious tumour shrinkage are unlikely to benefit from this intensive regimen and should probably be offered the gentler option of radiotherapy alone.

For people who do relapse with local recurrence then salvage surgical measures with either conventional resections or laser surgery may be helpful. As far as chemotherapy is concerned cytotoxic treatment is of limited value but the combination of cisplatin and fluorouracil is often used. For those patients who achieve a good response, and go on to relapse more than 3 months after completion of their treatment, then second line therapy with cytotoxics such as methotrexate or one of the taxanes may be worth a try.

Suggestions for Further Reading

Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet. 2008;371:1695–709.

Gold KA, Lee H-Y. Kim ES. Targeted therapies in squamous cell carcinoma of the head and neck. Cancer. 2009;115:922–35.

Mehanna H, West CML, Nutting C, Paleri P. Head and neck cancer. Part 1: epidemiology, presentation and prevention. Br Med J. 2010; 341:c4684.

Mehanna H, West CML, Nutting C, Paleri P. Head and neck cancer. Part 2: treatment and prognostic factors. Ibid c4690.

Skin Cancer

The principal types of skin cancer are basal cell carcinomas, squamous cell carcinomas and malignant melanoma. The great majority of skin cancers in the UK are either basal or squamous cell carcinomas, with more than 100,000 cases being diagnosed each year. Chemotherapy plays virtually no part in the management of these cancers, but occasionally topical application of fluorouracil cream (in concentrations of 0.5–5%) may be recommended for very superficial basal cell carcinomas.

Each year in Britain there are almost 12,000 new cases of malignant melanoma, making it the eighth commonest cancer in the UK. There are 1,800 deaths annually from malignant melanoma in Britain. The first line management of localised melanoma is surgery, with a wide local excision. The 5 year survival rate for men is about 80% and for women it is about 90%.

Numerous clinical trials have explored the role of adjuvant chemotherapy for the more advanced stages of localised disease, but none has yet shown a convincing benefit. For patients who are keen to explore adjuvant therapy the recommendation should be for them to enter an appropriate clinical trial.

Metastatic melanoma is a relatively chemoresistant disease. The drug which has been most extensively explored in this indication is the cytotoxic dacarbazine (DTIC). Used as a single agent this has produced partial response rates ranging from 15% to 30%, with complete responses in 3–5% of patients. However, there is no convincing evidence that treatment leads to any increase in survival. Similarly although some trials combining DTIC with other cytotoxics, or interferon, have claimed higher response rates there are still no clear data to support the view that life-expectancy is prolonged, compared to giving best supportive care.

This gloomy situation has improved recently with the introduction of two drugs which, for the first time, have actually shown an increase in survival in metastatic melanoma. The drugs are ipilimumab and vemurafenib. Ipilimumab is a

monoclonal antibody, given by intravenous infusion, which stimulates the immune system by blocking cytotoxic T-lymphocyte-associated antigen four and appears to increase median survival by about 4 months. Vemurafenib is an oral agent which targets a specific gene mutation (the BRAF V600E mutation) which is carried by about 50% of melanoma patients. In those who have the mutation about 50% have a response to vemurafenib and life expectancy does appear to be prolonged but by how much is uncertain at the present time.

Suggestions for Further Reading

Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364:2507–16.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363:711–23.

NICE. Improving Outcomes for People with Skin Cancers Including Melanoma. Department of Health. 2006.

Soft Tissue Sarcomas

There are about 2,200 new cases of soft tissue sarcoma each year in Britain, making up about 1% of all cancers. Just under 1,000 people die annually of the disease. The average age at the time of diagnosis is the early 60s, although these tumours may occur at any age. Soft tissue sarcomas make up a very diverse group of cancers (Table 3.3). Fifty percent of these growths occur in the limbs, 40% in the trunk or retroperitoneum, and 10% in the head and neck. The overall 5 year survival figure in the UK is between 50% and 60%, although the figures do vary considerably for different tumour types and sites, for example retroperitoneal soft tissue sarcomas tend to have a poorer outlook, largely because of their later presentation. The size and histological grade of the sarcoma are also important prognostic features with larger tumours,

Table 3.3 Relative incidence of soft tissue sarcomaa

	All sites (%)	Soft tissues only (%)
Leiomyosarcoma	24	12
Malignant fibrous histiocytoma	17	25
Liposarcoma	12	24
Dermatofibrosarcoma	11	2
Rhabdomysarcoma	5	5
Angiosarcoma	4	4
Nerve sheath tumours	4	6
Fibrosarcoma	4	5

[a]Soft tissue sarcomas may occur either in specific organs or in the soft tissues, and the incidence of the different types of sarcoma differs between the two sites. Approximately 50% of the sarcomas occur in soft tissues and 50% in specific organs. Among the latter the commonest are skin (28%), uterus (14%), the retroperitoneum (14%), stomach (8%), and small intestine (6%)

>5 cm, and high grade, grade III, cancers (which account for about 50% of these growths), faring worse.

Whenever possible surgery is the treatment of choice for these lesions, with removal of the primary cancer and a margin of at least 2 cm of surrounding normal tissue. When there is doubt about the completeness of the excision, or for larger, high grade lesions then post-operative radiotherapy is usually recommended.

Results suggest that adjuvant chemotherapy is of limited value. Local and distant relapse may be delayed by treatment but there are no convincing data that overall survival is increased. Clinical trials in this area are still continuing, particularly for larger lesions. Neoadjuvant, pre-operative chemotherapy is sometimes used for larger sarcomas, to try and improve the surgical outcome.

Soft tissue sarcomas tend to spread predominately to the lungs, and resection of isolated lung metastatases may sometimes be a treatment option in advanced disease. Cytotoxic

chemotherapy is of only limited value. The most active agents are doxorubicin and ifosfamide. When used as single agents they have a response rate of about 20%. Given in combination with dacarbazine, this figure rises to between 30% and 35%, but this is quite an aggressive regimen, most suitable for younger fitter patients. For those people who respond their life expectancy may be increased by a few months. Recently the alkylating agent trabectedin has been approved for use in people who relapse after ifosfamide or doxorubicin therapy and this drug may add a further few months to survival times.

One type of soft tissue sarcoma that merits special mention is gastrointestinal stromal tumour (GIST). These have been distinguished as a separate entity in the last decade, many previously being considered leiomyosarcomas. These are the commonest sarcoma of the gastrointestinal tract, with about 800 new cases in Britain each year. Surgery is the primary treatment wherever possible. Conventional cytotoxics are ineffective for more advanced stages of the disease, but more than 80% of these cancers carry a KIT gene mutation and are susceptible to the tyrosine kinase inhibitor imatinib. As a result these patients with advanced disease will gain a response lasting in excess of 2 years on average, and their median 5 year survival will be about 5 years, compared with only 1 year before imatinib was introduced. Studies have also been done looking at the use of imatinib in the adjuvant setting, following surgery. There is some evidence that it may reduce the risk of relapse but at the present time in the UK it has not been approved in this indication by NICE. Another tyrosine kinase inhibitor, sunitinib, is currently being evaluated for use in patients with relapsed or resistant GIST following imatinib therapy.

Suggestions for Further Reading

Clark MA, Fisher C, Judson I, Thomas JM. Soft-tissue sarcomas in adults. N Engl J Med. 2005;353:701–11.

DeMatteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localized primary gastro-intestinal stromal tumour: a randomized, double-blind trial. Lancet. 2009; 373:1097–104.

NICE technology appraisal guidance 196. Imatinib for the adjuvant treatment of gastrointestinal stromal tumours. NICE. 2010.
Toro JR, Travis LB, Wu HJ, et al. Incidence patterns of soft tissue sarcoma, regardless of primary site, in the surveillance, epidemiology and end results program, 1978–2001: an analysis of 26,758 cases. Int J Cancer. 2006;119:2922–30.
Trabectedin for the treatment of advanced soft tissue sarcomas. NICE technology appraisal guidance 185. NICE. 2010.

Primary Bone Sarcomas

There are about 450 new cases of bone sarcomas each year in Britain, making up about 0.2% of all cancers. About 200 people die annually of the disease. The majority of these cancers occur between the ages of 10 and 20, although there is a second peak in the over 60s which accounts for about 10% of cases. Primary bone tumours are commoner in men than women with a ratio of 3:2. The overall 5 year survival figure in the UK is just over 50%. Osteosarcomas are the commonest type of primary bone sarcoma, other types are Ewing's sarcoma, chondrosarcoma and spindle cell sarcomas (the latter being made up of a variety of tumour types, generally behaving in a similar way to osteosarcoma, and occurring in older people).

For osteosarcomas treatment is based on a combination of surgery and chemotherapy. Surgery is aimed at removing the primary tumour, which may involve an amputation. Cytotoxic chemotherapy is given pre-operatively (neoadjuvant therapy), to shrink the primary lesion, facilitating surgery, and is continued as post-operative adjuvant therapy. The most widely used treatment schedule is based on giving cisplatin, doxorubicin and high dose methotrexate followed by leucovorin rescue, ifosfamide is sometimes added to this regimen. A recent development has been the addition of the immunomodulator mifamurtide to the treatment protocol for young people, under the age of 30, and this appears to increase the chance of cure by about 10%.

For Ewing's sarcoma radiotherapy or surgery are used to treat the primary growth but adjuvant cytotoxic chemotherapy is then essential to maximise the chance of cure. In the UK and Europe favoured treatment schedules are vincristine, ifosfamide, doxorubicin and etoposide (VIDE) given every 3 weeks for six courses, or vincristine, ifosfamide and dactinomycin (VIA) given every 3 weeks for eight courses. In the North America combinations of either vincristine, doxorubicin and cyclophosphamide, or ifosfamide and etoposide tend to be preferred.

Treatment of chondrosarcomas and spindle cell sarcomas tends to be similar to that of osteosarcoma, although the chemotherapy schedules may be less intense as it is generally an older group of patients who are being treated.

Suggestions for Further Reading

Balamuth NJ, Womer RB. Ewing's sarcoma. Lancet Oncol. 2010; 11:184–92.

Geller DS, Gorlick R. Osteosarcoma: a review of diagnosis, management and treatment strategies. Clin Adv Hematol Oncol. 2010;8:705–18.

NICE technology appraisal guidance 235. Mifamurtide for the treatment of osteosarcoma. NICE. 2011.

Haematological Cancer

Acute Lymphoblastic Leukaemia

Acute lymphoblastic leukaemia (ALL) is a disease of progenitor cells for either B-cell or T-cell lymphocytes. In ALL these cells escape from normal growth control mechanisms and lose the ability to differentiate remaining as primitive blast cells, appearing in the peripheral blood and infiltrating the bone marrow.

There are about 550 new cases of ALL each year in Britain. Of these about two thirds are in children and adolescents, with a peak age of 3–4 years. In adults the median age

at diagnosis ranges from 25 to 37, this reflects a high incidence in young adults, and a second peak occurring in those over 75.

Progressive improvements in chemotherapy and supportive care over the last 50 years mean that in children the overall cure rate is in excess of 80%. Unfortunately the figure is far worse in adults, being about 40%. Age is a strong prognostic factor in adults, with older people faring worse. About 25% of adults, and 5% of children, with ALL will have leukaemic cells which carry the Philadelphia chromosome (see page 155).

There are a number of different subtypes of ALL and there are subtle differences in the treatment for each of these but in general for both adults and children there are four components to management: remission induction, consolidation or intensification, maintenance and CNS prophylaxis.

For children remission induction typically involves the use of a steroid (either prednisone, prednisolone, or dexamethasone), vincristine and asparaginase. For those with a poor prognosis, and most young adults, an anthracycline, usually daunorubicin will be added. For those adults with the Philadelphia chromosome the tyrosine kinase inhibitor, imatinib is added to their drug regimen. Treatment extends over 4–6 weeks, with the aim of destroying 99% or more of the leukaemic cells. The treatment is intensive and requires rigorous supportive care with red cell and platelet transfusions and infection prophylaxis, so it is done on an in-patient basis. The response to remission induction is a strong prognostic marker, with those who fail to gain a complete remission within 4 weeks having a poor outlook, however more than 95% of children and 80–90% of adults will go into remission.

For those who achieve a remission the next stage is intensification, or consolidation. This involves a variety of different regimens depending on the patient's age and the precise subtype of ALL. Typical treatments include high-dose methotrexate with mercaptopurine, or high-dose asparaginase with vincristine and a steroid, or a repeat of the original induction regimen. This phase usually lasts from 4 to 8 weeks.

An alternative at this stage, particularly for young adults, is an allogeneic stem-cell transplant.

Maintenance, or continuation therapy involves gentler, long-term chemotherapy, for between 2 and 3 years. The most widely used combination is daily oral mercaptopurine with weekly oral methotrexate. Adults with the Philadelphia chromosome will also continue imatinib.

Unless treatment is given between 30% and 50% of people who achieve a remission will relapse with CNS involvement by their leukaemia. It is impossible to predict who will develop this problem so treatment known as 'CNS prophylaxis' is almost universally given. This used to involve radiotherapy to the brain and spinal cord, but carried the risk of long-term complications including a degree of mental impairment and pituitary damage, so is now generally avoided. The usual alternative is intrathecal administration of methotrexate (see page 51). Depending on individual treatment protocols this may be given as part of remission induction, or intensification, or maintenance, or at all three stages of treatment.

Suggestion for Further Reading

Pui C-H, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med. 2006;354:166–78.

Pui C-H, Robison LL. Acute lymphoblastic leukaemia. Lancet. 2008;371:1030–43.

Acute Myeloid Leukaemia

Acute myeloid leukaemia (AML) is a disease of bone marrow stem cells, which produce red blood cells, neutrophils and platelets. In AML these cells escape from normal growth control mechanisms and lose the ability to differentiate remaining as primitive blast cells. When the bone marrow contains more than 20% of blast cells then AML is diagnosed. Failure of red cell and platelet formation lead to anaemia and bleeding

disorders and the absence of mature neutrophils leads to infection, which is the usual cause of death.

There are about 2,000 new cases of AML each year in Britain, with an average at diagnosis of 70. There are a number of different types of AML and 55% of people with the disease show specific cytogenetic abnormalities in their blast cells which allow not only for precise classification of their AML subtype but also give a guide to prognosis. Age is a major prognostic factor, with people over 55–60 faring far worse than younger adults. Performance status, and a number of biochemical measures, such as serum albumin, bilirubin and creatinine levels also influence outcome.

For younger adults, below the age of 60, the cornerstone of treatment is induction of complete remission which typically relies on a regimen of the cytotoxics daunorubicin (given intravenously on three consecutive days) and cytarabine (given by continuous intravenous infusion for 7–10 days). This combination will produce a complete remission (defined as <5% blasts in the bone marrow) in 65–75% of people. Other drugs which may be used in remission induction are etoposide, fludarabine and idarubicin. In one specific type of AML – acute promyelocytic leukaemia – the drug all-trans retinoic acid, vitamin A, is highly effective and is combined with an anthracycline cytotoxic in remission induction.

Once a remission has been achieved the next stage is consolidation therapy, which for good and intermediate prognosis individuals involves one of a number of regimens. Among the commonest of these are high dose cytarabine therapy or a repeat of two courses of induction therapy, followed by a course of m-amsacrine, cytarabine and etoposide followed by a final course of mitoxantrone and cytarabine. Once again all-trans retinoic acid is of value in acute promyelocytic leukaemia. Unlike acute lymphoblastic leukaemia there is no benefit in giving long-term maintenance therapy. For the poor risk group options include allogeneic stem cell transplants or experimental therapies. Depending on prognostic factors the overall cure rate for this age group lies between 20% and 75%.

The place of targeted therapies in AML is unclear. Clinical trials have focused on adding gemtuzumab to conventional

chemotherapy. Gemtuzumab is a conjugate of a monoclonal antibody, which targets the CD33 protein on the leukaemic cells, and a cytotoxic called calicheamicin. A major study in the USA showed that the drug not only failed to increase the remission rate but caused a number of life-threatening toxicities. However, two very recent European trials, using a different dosing schedule for the drug have actually shown an increase in survival figures with acceptable toxicity.

For older patients options include standard daunorubicin-cytarabine, possibly with gemtuzumab, experimental therapy or supportive care. Overall, however, the outcomes are disappointing with less than 10% of people being cured, and the average survival only stretching to 10 months. Certainly in the USA figures suggest of those people over 65 with AML only one third get chemotherapy and the overall median survival in this age group is only 3 months.

Suggestions for Further Reading

British Committee for Standards in Haematology. Guidelines on the management of acute myeloid leukaemia in adults. Br J Haematol. 2006;135:450–74.

Dohner H, Estey EH, Amodori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international panel on behalf of European LeukemiaNet. Blood. 2010;115:453–74.

Estey E, Dohner H. Acute myeloid leukaemia. Lancet. 2006;368: 1894–907.

Chronic Myeloid Leukaemia

As with acute myeloid leukaemia the underlying abnormality is overproduction of bone marrow stem cells. Ninety-five percent of people with chronic myeloid leukemia (CML) have a translocation between chromosomes 9 and 22, producing what is known as the Philadelphia chromosome. This translocation produces a fusion gene, BCR-ABL, which in turn generates a specific tyrosine kinase pathway which stimulates cell division.

There are about 650 new cases of CML in Britain each year, with an average of onset of 66 (although about 2% of cases occur in children). The disease goes through three phases. Firstly there is the chronic phase, which lasts about 3–5 years. Often a raised white cell count is the only abnormality during this time and symptoms are few, the condition frequently being diagnosed as the result of a routine blood test. This is followed by the accelerated phase which lasts anywhere from 2 to 15 months. During this time anaemia and splenomegaly develop causing symptoms of tiredness and abdominal discomfort, and an increased risk of infection and bleeding problems. Finally there is the blast crisis which lasts just a few months. This is essentially a transformation to an acute myeloid leukaemia, and is invariably fatal.

An allogeneic stem cell transplant is the only curative option for CML but most patients are too old for this to be considered. Over the last decade the drug treatment of CML has been transformed by the discovery of imatinib (Glivec). This is a signal transduction inhibitor which specifically blocks BCR-ABL tyrosine kinase activity. When given to people in the chronic phase of CML at a dose of 200 mg bd, more than 95% gain a response with nearly 90% still being alive after 5 years. Treatment with imatinib is continued indefinitely as even complete responders appear to be at risk of relapse if the drug is stopped. In order to be effective imatinib must be given as soon as possible after a diagnosis is made, treatment should be initiated in the chronic phase of the disease, even though there may be no symptoms, and not delayed until the condition progresses.

Recent randomised clinical trials with two of the newer BCR-ABL tyrosine kinase inhibitors, dasatinib and nilotinib, indicate that they are even more effective than imatinib in inducing remissions, including complete molecular remissions, with disappearance of all traces of the BCR-ABL gene from the blood. Whether these benefits are retained in the long-term remains to be seen and this uncertainty, together with economic concerns over the cost of the newer agents means that in most situations imatinib remains the first choice

therapy, but nilotinib and dasatinib do offer options for people who cannot tolerate imatinib or become resistant to it.

Treatment options for people who relapse on imatinib include interferon, cytotoxic chemotherapy with drugs like hydroxyurea (also known as hydroxycarbamide), busulphan, or cytarabine, or an allogeneic stem cell transplant, but the outcomes are uncertain.

Suggestions for Further Reading

Hehlmann R, Hochaus A, Baccarani M. Chronic myeloid leukaemia. Lancet. 2007;370:342–50.

Kantarjian H, Shah NP, Hochaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362:2260–9.

Saglio G, Kim D-W, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010; 362:2251–9.

Chronic Lymphocytic Leukaemia

In chronic lymphocytic leukaemia (CLL) the underlying abnormality is an overproduction of lymphocytes, which appear in the bone marrow, the circulating blood and as lymph node masses. Rather confusingly CLL is also be classified as form of low grade non-Hodgkin lymphoma.

There are about 4,500 new cases of CLL each year in Britain. The average age of onset is between 65 and 70. The overall median life-expectancy from the time of diagnosis is around 10 years, but there are wide individual variations. Between 75% and 80% of cases are asymptomatic and discovered as the result of routine blood tests, in the remainder the presenting symptoms are usually either enlarged lymph nodes, or tiredness due to anaemia.

The disease is normally indolent and asymptomatic patients often require no treatment initially. Indications for starting therapy include progressive bone marrow failure (with either anaemia or thrombocytopenia), enlarging lymph nodes or

progressive splenomegaly, a rapid increase in the number of circulating lymphocytes, or the onset of systemic symptoms such as weight loss or fever.

In contrast to CML there is no good evidence that treatment during the indolent phase of the disease improves the outcome so a watch and wait policy is usually appropriate, keeping treatment in reserve until symptoms develop. Traditionally first line active treatment has been based on single agent cytotoxic chemotherapy with the main choices being either chlorambucil, or fludarabine. Both these agents can be given orally, and result in remissions in 75–80% of patients, with about 30–40% of the being complete remissions, median survivals at 5 years are about 50%. On relapse further responses can often be obtained by either rechallenging with the original drug, or changing from one to the other. Other drugs that may be used are bendamustine and cladribine. This approach is still applicable for elderly, less fit people but for younger fitter patients other treatments are evolving.

In selected cases an allogeneic transplant is an option, and offers the only chance of cure, although the procedure is not without its risks and carries a mortality of about 20%. For most younger fitter people the preferred treatment will be combination therapy with cytotoxic drugs and a monoclonal antibody, the most widely used combinations being fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine and rituximab.

A special subgroup of patients can be defined as being 'high risk' and they have a deletion on chromosome 17 which renders them less sensitive to conventional treatments. If they are not suitable for an allogeneic transplant then monotherapy with the monoclonal antibody alemtuzumab or the FCR regimen can be tried but most people will go into clinical trials attempting to define the optimum therapy in this situation.

The enlarged lymph node masses which occur in CLL are very sensitive to radiotherapy and this may also be used to help control the disease in its more advanced stages. High dose steroid therapy may also be useful at this time.

Suggestion for Further Reading

Garcia-Escobar I, Sepulveda J, Castellano D, Cortes-Funes H. Therapeutic management of chronic lymphocytic leukemia. State of the art and future perspectives. Crit Rev Oncol Hematol. 2011;80:100–13.

Hallek M, Pflug N. State of the art treatment for chronic lymphocytic leukemia. Blood Rev. 2011;25:1–9.

Lymphomas

Lymphomas are traditionally divided into Hodgkin lymphoma, and non-Hodgkin lymphomas (NHL). Hodgkin lymphoma is named after the English pathologist, Thomas Hodgkin who first described the disease in the 1832, and is distinguished from other lymphomas by the presence of a specific type of abnormal B-lymphocyte: the Reed-Sternberg cell.

Hodgkin Lymphoma

There are about 1,400 new cases of Hodgkin lymphoma each year In Britain. The peak age of incidence is in young adults, although people of any age may be affected. Discovery of a swollen lymph node mass is the usual presenting feature but occasionally systemic symptoms: weight loss, fever, generalised itching, may dominate the picture. Forty years ago the condition was almost universally fatal but as the result firstly of wide-field radiotherapy, and then of developments in combination chemotherapy the overall cure rate is now in excess of 75%.

The choice of treatment depends on the specific cellular sub-type of Hodgkin lymphoma (Table 3.4), the stage of the disease (Table 3.5), and other prognostic factors. From these four subgroups can be identified:

Early favourable disease: non-bulky stage IA or II A. These patients used to be treated by wide field radiotherapy but increasing concerns about the risk of second malignancies and other long-term complications has led to an increasing preference for cytotoxic chemotherapy. Drug regimens that have

Table 3.4 Hodgkin lymphoma: cellular classification

Classical Hodgkin lymphoma
Nodular sclerosis
Mixed-cellularity
Lymphocyte depleted
Lymphocyte-rich classical
Nodular lymphocyte-predominant HL
This is a more indolent form of the disease, with a tendency to recur.

Table 3.5 The staging of Hodgkin lymphoma (simplified)

I. Involvement of a single lymph node region
II. Involvement of two or more lymph node regions on the same side of the diaphragm
III. Involvement of lymph node regions on both sides of the diaphragm
IV. Multifocal involvement of one or more extralymphatic organs
These stages may be subclassified with the suffix A or B. The B designation is given to people with one or more of the following symptoms:
unexplained weight loss of more than 10%
unexplained fever with temperatures above 38°C
drenching night sweats

been used include MOPP (nitrogen mustard, vincristine, procarbazine and prednisone), BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone), and ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine). Although MOPP was the pioneer combination which revolutionised the outcome in Hodgkin lymphoma both it and BEACOPP almost always lead to infertility, and also carry about a 3% risk of developing secondary acute leukaemia. By contrast ABVD has little effect on fertility and has <1% risk of leukaemia, so has become the preferred treatment. For these patients the treatment options are either 4–6 courses

of ABVD, or four courses of ABVD followed by radiotherapy to the involved lymph node sites, although recent trial results have queried the need for radiation.

Early unfavourable disease: stage IA or IIA with B symptoms, bulky disease or other adverse prognostic factors. Bulky disease is defined as lymph node masses greater than 10 cm in diameter, or mediastinal disease greater than one 33% of the thoracic diameter. The usually choice of treatment here is either 4–6 cycles of ABVD, or four cycles of ABVD followed by radiotherapy to the involved lymph node sites. These will result in a cure rate in excess of 80%.

Advanced favourable disease: stage III or IV disease with few adverse prognostic factors. The most widely used regimen is 6–8 cycles of ABVD, which may be followed by local radiotherapy if there was bulky disease. This will result in a cure rate of about 60%.

Advanced unfavourable disease: stage III or IV with poor prognostic factors. Options here include either 6–8 cycles of ABVD, or 6–8 cycles of BEACOPP. These will give a cure rate of up to 50%.

Non-Hodgkin Lymphoma

These are a diverse group of cancers and over the last 30 years more than 25 different systems have been suggested for their classification. Currently the most widely accepted system is the REAL/WHO classification. From a clinical viewpoint these various conditions can be grouped into indolent, or low grade NHL, or aggressive, or high grade NHL (Table 3.6). Between 60% and 80% of people with low grade NHL will survive 10 years or more and about 60% of those with high grade disease will be cured.

There are about 8,000 new cases of low grade NHL, and nearly 4,000 of high grade NHL, each year in Britain, and the incidence of the disease is steadily increasing at a rate of about 3% per year. Overall NHL is the sixth commonest cancer in the UK. Although the average age of onset is 55–60 people of any age may be affected. The clinical presentations vary widely but the discovery of enlarged lymph node masses

Table 3.6 Principal types of non-Hodgkin lymphoma, and their incidence

Low grade	
B-cell cancers	
Follicular lymphoma	22%
Extranodal marginal zone lymphoma (MALT lymphoma)	8%
B-cell small lymphocytic lymphoma/chronic lymphocytic leukaemia	7%
Nodal marginal zone lymphoma	2%
Lymphoplasmacytic lymphoma/ Waldentrom's macroglobulinaemia	1%
High grade	
B-cell cancers	
Diffuse large B-cell lymphoma	33%
Mantle cell lymphoma	6%
Burkitt's lymphoma	2%
T-cell cancers	
Mature (peripheral) T-cell neoplasms	8%
Precursor T-lymphoblastic lymphoma/ leukaemia	2%
Primary systemic anaplastic large cell lymphoma	2%

is the most common. The staging system for NHL is similar to that for Hodgkin lymphoma, although most people present with stage III or IV disease.

Although treatment varies with the individual type of NHL the broad principles of managing low grade and high grade disease are as follows:

Low grade disease: in a few instances the disease will be truly localised, confined to one or two groups of lymph nodes, and in this situation radiotherapy may result in a cure. In all other situations low grade NHL is usually incurable, although

the disease often progresses very slowly, with an overall median survival of about 10 years. Because of its slow progression and relative lack of symptoms some people may need no immediate treatment, and can enter a policy of watchful waiting, being regularly monitored with treatment being reserved until there are clear signs of disease progression. When treatment is needed cytotoxic chemotherapy is the usual choice, and options include oral chlorambucil as a single agent, or combination regimens with either CVP (cyclophosphamide, vincristine and prednisone), or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). There is now good evidence that adding the monoclonal antibody rituximab to any of these regimens increases the chance of remission and for those people who gain a benefit maintenance therapy with rituximab for up to 2 years has been shown to delay relapse and improve overall survival. Rituximab binds to a protein called CD20 which is found on the surface of normal and malignant B-cell lymphocytes. Malignant B-cell lymphocytes are the dominant cancer cell type in most types of low grade NHL. Although these drugs will bring about complete remissions for many people the disease will ultimately recur and re-treatment will be necessary.

High grade NHL: paradoxically, although it is more aggressive, the chances of a cure are greater with high grade than low grade NHL, with between 30% and 60% of people surviving long-term. Chemotherapy is the cornerstone of treatment with either CHOP, or R-CHOP (CHOP+ rituximab) for 4–8 courses. For some patients this may be followed by radiotherapy to the involved lymph node areas. For some younger patients, who have gone into remission but who are considered to be at high risk of relapse, bone marrow or stem cell transplantation may be considered.

Suggestions for Further Reading

Armitage JO. Early-stage Hodgkin's lymphoma. N Engl J Med. 2010;363:653–62.

Canellos GP, Niedzwiecki D, Johnson JL. Long-term follow-up of survival in Hodgkin's lymphoma. N Engl J Med. 2009;361:2390–1.

Lim SH, Johnson WM. Chemotherapy: advanced Hodgkin lymphoma – balancing toxicity and cure. Nat Rev Clin Oncol. 2011;8:634–6.
Lowry L, Hoskin P, Linch D. Developments in the management of Hodgkin's lymphoma. Lancet. 2010;375:786–8.
Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited stage Hodgkin's lymphoma. N Engl J Med. 2012;366:399–408.
McNamara C. Evolution of first-line therapy for symptomatic advanced-stage follicular lymphoma. Oncol News. 2012;6:200–1.
NICE Technology Appraisal Guidance 137. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma. NICE. 2008.

Multiple Myeloma

The underlying abnormality in multiple myeloma is a proliferation of abnormal plasma cells (plasma cells are derived from B-lymphocytes, and are responsible for antibody production). These settle in the bone marrow and cause destruction of the surrounding bone, leading to pain and fractures. Normal plasma cells are involved in antibody formation and produce immunoglobulins, their malignant counterparts usually produce abnormal amounts of specific immunoglobulins and the high concentrations of these can lead to complications such as renal failure.

There are about 3,300 new cases of multiple myeloma each year in Britain. The median age at presentation is about 70, and fewer than 2% of patients are diagnosed under 40. Bone pain is the commonest presenting symptom. The condition is incurable but survival times are very variable, ranging from a few months to more than 20 years.

Some people may be asymptomatic when multiple myeloma is first diagnosed, and for them it is often safe to withhold treatment until there is evidence of disease progression, which may be anywhere from 1 to 3 years. Once treatment is indicated the choice of therapy is determined by a number of factors, including the patient's age and general fitness.

For younger patients, below the ages of 55–65, some form of high-dose chemotherapy and a stem cell transplant may be considered. In this situation the induction treatment has relied on cytotoxic drug combinations such as VAD (vincristine, doxorubicin and dexamethasone), but there is evidence from a number of trials that adding one of the newer agents such as thalidomide, lenalidomide or bortezomib to this regimen can improve the outcome increasing the chance of 5 year survival to over 50%. As yet no single regimen has emerged as the treatment of choice.

The majority of people, however, a stem cell transplant is not going to be an option because of their age and fitness. In this situation the traditional approach is gentler oral treatment with melphalan and prednisolone. Once again recent trials have shown that adding either thalidomide, lenalidomide or bortezomib to this combination boosts complete response rates and 3 year survival to over 80%.

Bone pain is a major problem in multiple myeloma. Successful chemotherapy often eases the problem but for those people where symptoms persist localised radiotherapy (usually only requiring a single low dose treatment) or bisphosphonates given orally or by intravenous infusions every 4–6 weeks may be very beneficial. Bisphosphonates also help reduce the risk of bone fractures and spinal cord compression.

Suggestions for Further Reading

Gay F, Palumbo A. Management of older patients with myeloma. Blood Rev. 2011;25:65–73.

Hicks LK, Haynes AE, Reece DE. A meta-analysis and systematic review of thalidomide for patients with previously untreated multiple myeloma. Cancer Treat Rev. 2008;34:442–52.

Raab MS, Podar K, Breitkreutz I, et al. Multiple myeloma. Lancet. 2009;374:324–39.

San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359:906–17.