Medical management of colorectal cancer

By Dr David Ransom, Oncologist

Over the past decade there has been a steady improvement in survival rates for patients with colorectal cancer. Early detection is the key, so the introduction of faecal occult blood screening in Western Australia should lead to a further decline in mortality for this common cancer. For those diagnosed with metastatic colon cancer, advances in medical management over the last 20 years have increased average survival from about 6 months to 20 months post-diagnosis and a few patients are living four to five years before exhausting all therapeutic options. There is still room for considerable improvement in the efficacy and tolerability of the drugs available.

Localised rectal cancer

A study of pre-operative versus post-operative chemotherapy/radiotherapy in localised rectal cancer showed that pre-operative chemotherapy is clearly superior. Local recurrence was halved from 13% to 6%, and the incidence of serious side effects decreased from 40% to 27%. This is now adopted as standard therapy with virtually all patients with large tumours (T3 and T4) having five weeks' of radiotherapy and infusional 5-fluruouracil. Patients then have a break for 5 to 6 weeks prior to undergoing surgery.

Adjuvant therapy for high-risk stage 2 and stage 3 colon cancer

Adjuvant chemotherapy is administered after surgery with the aim of eliminating micrometastatic disease.

There are two choices for stage 3 (lymph node positive) colon cancer, capecitabine (XelodaTM) or oxaliplatin/5 fluruouracil. Capecitabine is in tablet form, is metabolised to 5 fluruouracil, and is PBS subsidised for stage 3 colon cancer. Patients much prefer the tablets, however there is still the potential for serious side-effects and an increased chance of medication errors.

The other regimen is FOLFOX, which is a two-drug combination of oxaliplatin and 5-fluorouracil given as a 48-hour IV infusion on a 14-day cycle. This regimen may be less convenient for the patients but it is superior to 5-fluorouracil alone and probably capecitabine. When 5 fluorouracil and oxaliplatin/5-flurouracil were compared in a randomised study, there was an absolute increase in survival by approximately 3% in favour of FOLFOX.

Oxaliplatin carries a risk of acute and long-term neurotoxicity. Approximately 5% of patients have moderate long term tingling and 0.5% of patients have numbness that interferes with function after completing their treatment. The neuropathy tends to improve for two to three years after finishing therapy.

Stage 2 (i.e. lymph node negative) patients generally have a good prognosis and are therefore less likely to benefit from adjuvant chemotherapy. Capecitabine and oxaliplatin are not PBS listed for stage 2 disease.

Indications of a poor prognosis include T4 staging (i.e. tumour invades through peritoneal serosa or into adjacent organ), lymphovascular invasion and poorly differentiated tumours. These patients may benefit from chemotherapy for six months, such as 5 fluorouracil/ leucovorin.

Metastatic colorectal cancer

Capectabine/5 fluorouracil, oxaliplatin and irinotecaan remain the three most active chemotherapy drugs in metastatic colorectal cancer. The best results are obtained if patients receive all three drugs.

Usually, the initial regimen is oxaliplatin plus 5fluorouracil/capectabine. If the tumour is well controlled the oxaliplatin is stopped after 4 to 6 months because of the risk of neurotoxicity. Patients with low volume metastatic disease could stop chemotherapy entirely (chemotherapy holiday) but patients with high volume metastatic disease should continue 5FU/capectabine and at progression either restart oxaliplatin or switch to irinotecan.

Recently, bevacizumab became PBS subsidised as first line treatment for metastatic colon cancer given in combination with chemotherapy. Bevacizumab is an antibody against vascular endothelial growth factor (VEGF), which is a molecule necessary in the process of angiogenesis. The addition of bevacizumab to standard chemotherapy improves survival by a range of 2-4 months. There are usually few side effects but potential problems include hypertension, proteinuria, renal impairment and delayed wound healing.

Cetuximab and panatumumab are antibodies that are useful in metastatic colon cancer. Both are active against epithelial growth factor receptor and also have been shown to improve survival in patients with metastatic colon cancer. The TGA indication for cetuximab is after other chemotherapies have failed. Recent analysis has shown that patients whose tumours carry K-ras mutations do not benefit from this drug (i.e. about 40% of all patients with colorectal cancer). However, for patients with a K-ras wild type these antibodies remain active even after multiple previous chemotherapies. Currently there is no PBS subsidy for cetuximab or pantumumab, resulting in significant out-of-pocket expenses for the patients. The major side effect is rash, which tends to peak at 4 to 8 weeks after commencing treatment and then slowly improve, however most patients have persistent skin problems. These drugs also affect distal renal tubules, causing hypomagnesaemia. ■