Capecitabine (Xeloda®) is an oral fluoropyrimidine, which inhibits thymidylate synthetase (TS), after activation by thymidine phosphorylase (TP). It is currently approved in Australia for use in metastatic breast cancer after failure of standard therapy, and for advanced or metastatic colorectal cancer (CRC). Trials are underway examining the efficacy of capecitabine in all the other malignancies currently treated with 5-Fluorouracil (5-FU), and in combination with other agents.

**Biological activity**

Thymidine phosphorylase is a tumour-associated angiogenic growth factor that induces neovascularisation and decreases apoptosis. As tumour cells have higher doses of TP than normal cells, capecitabine is preferentially activated to 5-Fluorouracil in tumour cells. This has the advantage of tumour selectivity with increased tumour drug concentrations but lower systemic 5-FU levels. Tumour selectivity was confirmed in a colorectal cancer trial, which demonstrated that after capecitabine administration the concentration of 5-FU in the tumour was 3.2 times greater than in adjacent tissue and 21 times higher in the tumour than in plasma. Preclinical studies suggest that there is a correlation between increased tumour biochemical markers (TP, DPD) and sensitivity to capecitabine. If this proves to be correct this may allow for individualisation of treatment. Further to this, at the annual meeting of the American Society of Clinical Oncology 2001 Park et al presented a paper reporting that patients who are homzygous for double repeats of the 28 base-pair sequence in the TS gene (SS) respond much better to capecitabine with 80% responding compared to 10% with S/L and 14% with L/L variants. They conclude that genotyping of patients may be helpful to select patients likely to benefit from capecitabine.

**Pharmacology**

Capecitabine taken daily or twice daily has been shown to provide a steady plasma or tissue level to mimic continuous 5-Fluorouracil (5FU) without the inconvenience of requiring central venous access. It is a prodrug that is metabolized via a three-step enzymatic process to the active agent fluorouracil. The capecitabine is rapidly and extensively absorbed through the wall of the intestine and is then hydrolysed in the liver by carboxylesterase to 5'-deoxy-5-fluorocytidine (5'-DFCR). It is then converted by cytidine deaminase to 5'-deoxy-5-fluorouridine (5'-DFUR) in the liver and/or tumour cells. The 5'-DFUR is then activated by thymidine phosphorylase (TP) within tumour cells to 5-FU where it is subsequently converted to false nucleotides leading to inhibition of the enzyme thymidylate synthase (TS) and RNA & DNA disruption.

Phase II and III trials have confirmed that Capecitabine at 1250mg/m² twice daily after food, for two weeks followed by a one-week rest period appears to be the most beneficial dosing schedule. The tablets are available in 150mg and 500mg doses. Mild to moderate hepatic impairment does not significantly alter the pharmacokinetics of capecitabine and therefore dose modification is not necessary. Capecitabine is contraindicated in severe renal impairment and moderate impairment is likely to require dose modification.

Capecitabine can interact with both warfarin and phenytoin making careful monitoring essential. Altered coagulation parameters and serious bleeding have been reported with capecitabine and concomitant warfarin. Capecitabine should not be used in pregnancy.

**Capecitabine in advanced breast cancer**

Phase II trials in patients with metastatic breast cancer have shown that capecitabine is efficacious following taxane therapy. Blum et al conducted a trial of capecitabine in 163 women with metastatic breast cancer who had progressed with paclitaxel. Ninety percent of the patients had previously received anthracyclines and 82% had been treated with 5-FU. They demonstrated a 20% objective tumour response with capecitabine including three complete responses and achieved stable disease in a further 43% of patients. Progressive disease was reported in 31% of patients. The median duration of response was 7.9 months, median time to progression three months, and median survival 12 months. A Clinical Benefit Response assessing pain, analgesic consumption and Karnofsky Performance Status was applicable to 147 patients with 20% reporting an improvement in each parameter and 31% of patients remaining stable.

Blum et al reported that generally the drug was well tolerated; however grade three to four toxicities included diarrhea (14%), hand-foot syndrome (10%), fatigue (7%), stomatitis (7%), nausea (4%) and vomiting (4%). Neutropenia occurred in only three percent of patients and no alopecia was reported. Grade four toxicity occurred in 3.7% of patients. Seven percent of patients ceased capecitabine due to adverse effects and 55% required dose reductions.

Hand-foot syndrome (HFS) or palmar plantar erythrodysesthesia is a cutaneous reaction that has been reported after use with capecitabine as well as with 5-FU, doxorubicin, vinorelbine and cytarabine. Parasthesiae of the hands and feet is classified as grade one toxicity. This progresses to oedema and erythema of the palms and soles in grade two toxicity and involves desquamation of the hands and feet with ulceration in grade three toxicity. This condition can be extremely painful, impairing walking and limiting hand function. Treatment should primarily target prevention of serious toxicity with early detection of the syndrome. This highlights the importance of patient education prior to commencing treatment so that the patient, and the health professionals involved, recognises the early signs and symptoms of capecitabine toxicities and is able to implement timely management of toxicities. Mild cases generally only require an emollient although pyridoxine and steroids can also be used to treat more advanced HFS. Grade two toxicity requires interruption of treatment until the HFS has fully resolved with dose reduction if the toxicity reappears.

A phase II trial of 95 women aged 55 or older who had had no prior cytotoxic treatment for their metastatic breast cancer were randomised to either capecitabine or CMF. The capecitabine arm had an objective response rate of 30% (CI 14-37%) compared with 16% (CI 15-33%) in the CMF arm.
There were five complete responses in the capecitabine group. Median survival was 21.6 vs 17.2 months and median time to progression was 4.1 compared with 3.0 months. A study to confirm these findings of first line activity in elderly patients is planned by the Australia and New Zealand Breast Cancer Trials Group.

Encouraging single agent activity with modest toxicity has encouraged the exploration of capecitabine in combination therapy. Initial reports of a phase III study compare the combination of capecitabine and docetaxel vs docetaxel alone in women with metastatic breast cancer who had previously failed anthracycline treatment. The trial reports increased survival with a 22.5% reduced risk of death (p=0.013), an increased median survival of three months over docetaxel alone (median survival 14.5 vs 11.5 months) and increased median time to progression (6.1 vs 4.2 months, p=0.001). Tumour response rate was 32% vs 22% (p=0.009). The combination treatment had more adverse events with an increase in diarrhoea, stomatitis, HFS and nausea and vomiting. The taxotere alone arm reported increased neutropenic sepsis, myalgias and arthralgias

Capecitabine in advanced colorectal cancer

Two phase III trials in metastatic colorectal cancer have been conducted comparing capecitabine with intravenous 5-Fluorouracil/leucovorin (5-FU/FA) The trials used the Mayo Clinic regimen of 5-FU with bolus IV injection daily for five days in four week cycles. The trials were prospectively integrated, giving data on 1,200 patients. There was a significant improvement in response rate in the capecitabine arm (25.7% vs 16.7% in the 5-FU/FA arm (p<0.002)); however no significant difference in time to disease progression (median 4.6 vs 4.7 months respectively) or overall survival (12.9 vs 12.8 months). HFS was more common in the capecitabine arm, however only half the patients required treatment. Stomatitis, diarrhoea, nausea, stomatitis, neutropaenia and alopecia were all significantly more frequent in the 5-FU/FA arm. Vomiting and fatigue were similar in both groups. Fewer patients required dose modification or hospitalisation for treatment related toxicity in the capecitabine arm.

In metastatic CRC trials are currently investigating capecitabine and weekly irinotecan as first line treatment, and capecitabine and oxaliplatin. Adjuvant studies have been completed and results are awaited.

In summary the oral administration of fluoropyrimidines appear to offer at least equivalent efficacy to intravenous 5-FU but with significantly less toxicity, increased patient acceptance with the advantage of a home based treatment, and possibly a reduction in the total healthcare costs associated with 5-FU sensitive tumours.

References

6 Xeloda Product Monograph