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Review paper

Capecitabine: a novel agent for the treatment of solid tumors

PG Johnston[1] and S Kaye[2]
[1]Department of Oncology, The Queen's University of Belfast, Belfast City Hospital, Belfast BT9 7AB, UK.
[2]Royal Marsden Hospital, Sutton SW3 6JJ, UK.

Although 5-fluorouracil (5-FU) has been used to treat breast and colorectal cancers for several decades, bolus 5-FU has disappointing efficacy. Prolonged infusion schedules and biomodulation with leucovorin have resulted in improved response rates, but these have not translated into significant improvements in survival in patients with metastatic disease. Furthermore, prolonged infusion is inconvenient for patients and can result in medical complications. New oral fluoropyrimidines, including capecitabine, are promising alternatives to i.v. 5-FU. Capecitabine generates 5-FU preferentially within tumors through exploitation of the high intratumoral activity of thymidine phosphorylase. The tumor selectivity of capecitabine has been confirmed in a clinical study of colorectal cancer patients. Clinical trials have shown that capecitabine is an effective, well-tolerated treatment for breast and colorectal cancer, with response rates of 20–26% in anthracycline- and taxane-pretreated metastatic breast cancer. As first-line monotherapy, capecitabine produces response rates of 25–27% in metastatic colorectal cancer and 30% in metastatic breast cancer. In all studies to date, capecitabine has been well tolerated, with adverse events typical of infusional 5-FU and manageable with treatment interruption/dose modification. Myelosuppression and alopecia are rare. Capecitabine is also being investigated in other solid tumors (including ovarian, pancreatic and gastric cancers) as adjuvant monotherapy in breast and colorectal cancer, and in combination with other cytotoxic agents. Results of ongoing trials are eagerly awaited. [© 2001 Lippincott Williams & Wilkins.]

Key words: 5-Fluorouracil, breast cancer, capecitabine, colorectal cancer, fluoropyrimidines, thymidine phosphorylase.

Introduction

Since 5-fluorouracil (5-FU) was first introduced more than 40 years ago, it has become standard therapy for a number of solid tumors, either as a single agent or in combination with other cytotoxic agents or biomodulators.[1–3] Nevertheless, 5-FU therapy has several limitations, including a relatively short half-life and significant toxicities that require dose reduction in 30–40% of patients following bolus administration.

This paper reviews the clinical use of 5-FU in the treatment of solid tumors, and discusses strategies for improving the efficacy and safety of 5-FU. It also discusses the developing role of the oral fluoropyrimidine capecitabine, a novel fluoropyrimidine carbamate that generates 5-FU preferentially in tumor tissue.

Mechanisms of 5-FU action

5-FU is metabolized to active nucleotides which mediate cytotoxicity.[4] The 5-FU metabolite fluorodeoxyuridine monophosphate (FdUMP) inhibits the enzyme thymidylate synthase (TS), using reduced folate as a cofactor. TS catalyzes the *de novo* synthesis of thymidine nucleotides and TS inhibition causes the formation of unbalanced pools of deoxynucleotide triphosphates, the immediate precursors for DNA synthesis. The resulting disruption to DNA synthesis and repair leads to an increase in DNA strand breaks. FdUMP can also undergo phosphorylation to the triphosphate form, which can be incorporated as a false nucleotide into DNA.[5] In addition, another 5-FU metabolite, fluorouridine triphosphate (FUTP), can be incorporated as a false nucleotide into RNA causing inhibition of protein synthesis.[6]

Efficacy of 5-FU-based therapy

5-FU, either alone or in combination with other cytotoxic agents, is used widely for the treatment of

Correspondence to PG Johnston, Department of Oncology, The Queen's University of Belfast, University Floor, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB, UK.
Tel: (+44) 28 9026 3911; Fax: (+44) 28 9026 3744;
E-mail: oncology@qub.ac.uk

several solid tumor types, including colorectal, breast, and head and neck cancers.

Metastatic colorectal cancer

5-FU is the mainstay of chemotherapy for colorectal cancer and is effective in the adjuvant setting or for the treatment of advanced/metastatic disease.[7] Response rates with 5-FU monotherapy as first-line treatment for colorectal cancer are typically in the range 10–20% and median survival is less than 12 months.

5-FU has a short plasma half-life and, following bolus administration, plasma concentrations rapidly fall below the cytotoxic threshold. Attempts to increase the activity of i.v. bolus 5-FU have included schedule modifications, the use of protracted infusion regimens, and the addition of biochemical modulators such as leucovorin, levamisole, *N*-(phosphonacetyl)-L-aspartate (PALA) and interferons.[2] Of these, leucovorin is the most effective and its use is widespread.[8] When leucovorin is added to 5-FU, the intracellular pools of reduced folate are expanded and the complex formed between TS, FdUMP and reduced folate is stabilized, resulting in more effective TS inhibition. Randomized trials have demonstrated that, compared with 5-FU alone, combination therapy with 5-FU and leucovorin is associated with improvements in tumor response, survival and quality of life in patients with advanced colorectal cancer.[9,10] However, a meta-analysis of nine trials comparing combined 5-FU plus leucovorin therapy with 5-FU alone found no statistically significant difference in median survival, despite a significantly improved tumor response rate with combination therapy.[11]

Another important approach to improving the efficacy of bolus 5-FU is prolonged infusion. Randomized trials in advanced colorectal cancer have shown that continuous or protracted infusion of 5-FU, with or without leucovorin, results in superior response rates compared with i.v. bolus 5-FU.[12–15] However, these trials demonstrated either no impact or only a modest improvement in survival compared with bolus 5-FU. Similarly, a meta-analysis indicated that continuous infusion leads to only a small overall survival benefit, with a median survival of 12.1 versus 11.3 months for continuous infusion 5-FU and bolus 5-FU, respectively.[16]

Despite the improvements in colorectal cancer treatment that have been achieved with 5-FU schedule modification and biomodulation, there is no universal agreement on the optimal regimen or the standard method for administering 5-FU in metastatic colorectal cancer. However, it is generally agreed that a more convenient alternative to i.v. 5-FU is required, enabling patients to maintain as normal a lifestyle as possible.

Metastatic breast cancer

The primary goals of treatment for metastatic breast cancer are symptom palliation, reduction of tumor-related symptoms, improved inconvenience for patients, enhanced or maintained performance status and, ultimately, prolonged survival without substantial toxicity.

5-FU is frequently used in combination with other cytotoxic agents as first-line treatment for metastatic breast cancer. The most effective 5-FU-based combination regimens are FAC (5-FU, doxorubicin and cyclophosphamide), FEC (5-FU, epirubicin and cyclophosphamide) and CMF (cyclophosphamide, methotrexate and 5-FU).[17] Objective responses occur in 50–80% of women with FAC and 40–60% of women with CMF, and both regimens provide significant palliation with acceptable levels of toxicity.

In the last decade, the range of treatment options for advanced breast cancer has increased with the introduction of vinorelbine and the taxanes, paclitaxel and docetaxel.[17] Monotherapy with these agents has been shown to be at least as effective as combination CMF. Regimens combining a taxane with an anthracycline are even more effective, with response rates of 40–94% and complete remission rates of 12–41%.[18] Taxanes are effective in the treatment of anthracycline-resistant disease, leading to response rates of 20–40% and survival of 10–12 months.[19] Dose-limiting toxicities include neutropenia, neuropathy and cardiopathy, which can lead to congestive heart failure.[20] At present, the taxanes and vinorelbine are used routinely for second- and third-line therapy, and are being used increasingly as first-line or adjuvant treatment for breast cancer. The use of these highly active chemotherapeutic agents earlier in the disease course has resulted in an increase in the number of patients presenting with metastatic disease that has progressed during or following therapy with standard agents, including the taxanes. Until recently there were no established treatment options for patients pretreated with taxanes and there was an unmet medical need for new, effective, well-tolerated agents in this setting.

Side effects of 5-FU

Bolus i.v. 5-FU is typically associated with dose-limiting myelosuppression and gastrointestinal toxicities such as nausea, vomiting, diarrhea and stomatitis. These can be severe and often necessitate hospitalization.[2,21] Continuous infusion 5-FU is better tolerated than bolus schedules: myelosuppression is less frequent and the main dose-limiting toxicities are stomatitis and diar-

rhea. Palmar–plantar erythrodysesthesia (hand–foot syndrome) may also be dose limiting.[2] Several studies have compared the toxicity of bolus or continuous infusion 5-FU in patients with colorectal cancer. An early study indicated that leukopenia occurred in 31% of patients receiving bolus 5-FU and was absent in patients receiving 5-FU infusion.[22] Severe mucositis occurred in 16 and 65% of patients receiving bolus or infused 5-FU, respectively. Six percent of patients in the bolus group died from drug-related causes and there were no deaths in the infusion group. Similarly, in a study reported by Lokich *et al.*,[12] 20% of patients receiving bolus 5-FU experienced severe leukopenia and there were four sepsis-related deaths. In contrast, the incidence of severe leukopenia was only 1% in the continuous infusion group.

Despite the benefits associated with continuous infusion 5-FU, bolus administration is widely used. There are several drawbacks with continuous infusion regimens, including the need for indwelling venous catheters and portable infusion pumps, which are costly and are labor-intensive for medical staff.[23] These devices can be painful for the patient and are associated with complications such as infections, bleeding and pneumothorax.[8,23,24] A prospective study showed that 13% of patients experienced complications during the insertion of central venous catheters for ambulatory chemotherapy.[25] Overall, complications (most commonly infection or thrombosis) led to catheter removal in 19% of patients. A study by Hansen *et al.* of patients with colorectal cancer indicated that up to 40% of patients may experience venous access-related complications.[26]

Convenience and the maintenance of patient quality of life are major considerations in palliative chemotherapy. Patients with incurable solid tumors prefer to be treated at home rather than as inpatients[27] and most prefer oral agents to i.v. therapy.[28,29] However, patients are not willing to sacrifice efficacy for their preferences. New chemotherapeutic agents with greater efficacy, improved tolerability, and acceptable administration schedules are needed. Moreover, increasing emphasis is being placed on patient quality of life and the cost-effectiveness of treatments. Effective oral chemotherapy agents may be advantageous, providing convenient, home-based therapy that is more acceptable to patients and more cost-effective for healthcare providers.

Oral fluoropyrimidines

5-FU is unsuitable for oral administration because of its unpredictable and highly variable bioavailability and rapid degradation in the gastrointestinal tract. Recently, a number of 5-FU prodrugs and dihydropyrimidine dehydrogenase (DPD) inhibitors have been developed as oral agents.

UFT is a combination of tegafur, a 5-FU precursor, and uracil in a 1:4 fixed molar ratio. Uracil is a competitive inhibitor of DPD and reduces the rate of 5-FU breakdown.[30] UFT has been investigated in combination with leucovorin in the treatment of patients with metastatic colorectal cancer. A randomized, phase III trial comparing UFT/leucovorin with standard i.v. bolus 5-FU/leucovorin was conducted in 816 patients with metastatic colorectal cancer. The primary endpoint of the trial was median survival, which was found to be equivalent in the two treatment arms (12.4 months for UFT/leucovorin versus 13.4 months for 5-FU/leucovorin).[31] Response rates were 12% with UFT/leucovorin and 15% with 5-FU/leucovorin. Time to disease progression was inferior in patients receiving UFT/leucovorin (3.5 months versus 3.8 months with 5-FU/leucovorin).

S-1 is a fixed mixture of tegafur and two modulators: 5-chloro-2,4,-dihydroxypyridine, which inhibits DPD, and oxonic acid, which inhibits 5-FU phosphorylation in the gastrointestinal tract. Oxonic acid is included with the aim of reducing the incidence of dose-limiting diarrhea.[32] Japanese phase II studies have demonstrated that S-1 is active in gastric, colorectal, breast, and head and neck cancers.[33–36] However, despite the presence of oxonic acid, there was a high incidence of dose-limiting diarrhea. Diarrhea was also the dose-limiting toxicity in a European phase I dose-finding trial in patients with solid tumors.[37] In a recent phase II trial of S-1 40 mg/m^2 twice daily in patients with previously untreated metastatic colorectal cancer, the response rate was 35% in 62 eligible patients, with a median survival of 12 months.[38] Grade 3/4 neutropenia occurred in 13% of patients; gastrointestinal toxicities were also relatively common.

Eniluracil, a uracil analog, is a potent, irreversible inhibitor of DPD.[39] The addition of eniluracil to oral 5-FU improves the absorption and bioavailability of 5-FU.[40] In a phase II study of oral eniluracil in combination with oral 5-FU, with or without leucovorin, the response rate was 21% in 75 patients with previously untreated solid tumors.[41] Myelosuppression was the dose-limiting toxicity and neutropenic sepsis was reported in 14% of patients.

Eniluracil has also been evaluated in combination with oral 5-FU as first-line treatment for metastatic breast cancer. A phase II study in 33 previously untreated patients revealed a response rate of 48% and a median duration of response of 14 months. The median time to disease progression was 7 months.[42]

Adverse events included diarrhea (42%), nausea (27%), mucositis (18%) and hand–foot syndrome (15%). In patients with metastatic breast cancer pretreated with anthracyclines and taxanes, eniluracil plus oral 5-FU resulted in a 16% overall response rate in a phase II study.[43] As in the first-line setting, the principal toxicities were nausea (33%) and diarrhea (30%).

Capecitabine

Capecitabine is an oral fluoropyrimidine carbamate that was rationally designed to mimic continuous infusion 5-FU and generate 5-FU preferentially within tumor tissue.[44] The aim of tumor-selective delivery of 5-FU was to enhance efficacy and improve safety by minimizing systemic exposure to 5-FU. Capecitabine is absorbed unchanged through the gastrointestinal wall and is converted to 5-FU via a three-step enzymatic cascade (Figure 1). It is hydrolyzed in the liver by carboxylesterase to the intermediate, 5′-deoxy-5-fluorocytidine (5′-DFCR). The next step occurs in the liver and/or tumor tissue, where cytidine deaminase converts 5′-DFCR to 5′-deoxy-5-fluorouridine (5′-DFUR). Finally, 5′-DFUR is converted to 5-FU by thymidine phosphorylase (TP). TP is significantly more active in tumor tissue than in normal tissue, resulting in tumor-selective generation of 5-FU.[44]

The tumor selectivity of capecitabine has been confirmed in a pharmacodynamic study of 19 patients undergoing resection for colorectal cancer.[45] Patients received capecitabine 1255 mg/m^2 twice daily for 5–7 days before resection. Following administration of capecitabine, the mean concentration of 5-FU was more than 3 times higher in primary tumor tissue than in adjacent healthy tissue. Similarly, the 5-FU concentration was more than 21 times higher in tumor tissue than in plasma.

The tumor selectivity of capecitabine resulted in improved efficacy compared with non-selective fluoropyrimidines in human cancer xenograft models.[46] The antitumor activity of capecitabine, 5-FU and UFT administered at their maximum tolerated doses was compared in xenograft models of human colon, cervix, bladder, ovary, breast and prostate cancer. Capecitabine inhibited tumor growth by more than 50% in 75% of the 24 tumor models tested. In contrast, 5-FU and UFT were effective in only 4 and 21% of models, respectively.

Another preclinical study demonstrated that the activity of TP in tumor tissue, and more particularly the ratio of TP to DPD, can be used to predict the sensitivity of tumors to capecitabine.[47] The ability to predict sensitivity potentially enables individualized treatment that could spare patients from ineffective treatment and unnecessary toxicity.

The activity of TP in tumor tissue is increased following exposure to a number of cytotoxic agents. A preclinical study demonstrated that administration of taxanes causes a dose- and time-dependent upregulation of TP activity in human colon cancer xenografts.[48] Other therapies that have been shown to upregulate tumor TP activity include mitomycin C, cyclophosphamide, interferon-α and radiotherapy.[48–51]

Clinical studies with capecitabine

Breast cancer

Capecitabine is active in patients with metastatic breast cancer that has progressed during or following treatment with standard therapy, including taxanes.[52,53] Two multicenter phase II studies including a total of 236 patients have demonstrated the efficacy of capecitabine in anthracycline- and taxane-pretreated metastatic breast cancer.[52,53] In this heavily pretreated

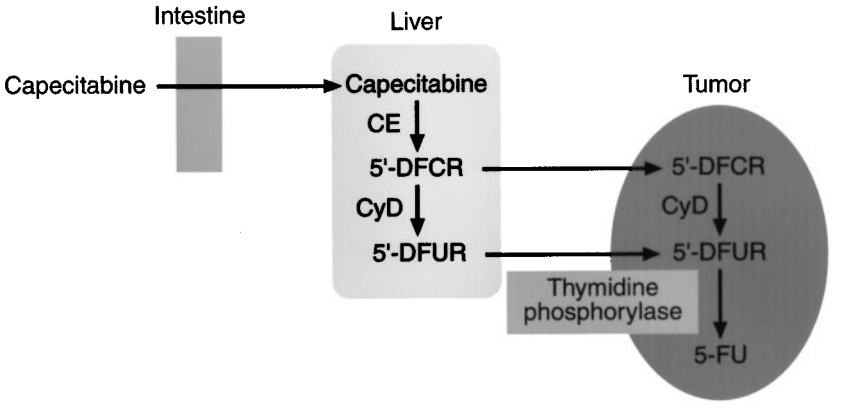

Figure 1. Enzymatic activation of capecitabine.

patient population, capecitabine resulted in response rates of 20–26%, with a 29% response rate in a retrospectively defined subpopulation of 42 patients refractory to both paclitaxel and doxorubicin.[52] Median overall survival was in excess of 12 months in both studies.[52,53] Capecitabine therapy also provided palliative relief.[52] In the first study, 47% of the 51 patients with considerable pain at baseline experienced a durable, 50% reduction in pain intensity.

Two randomized, phase II studies have shown that capecitabine is also effective in anthracycline-pretreated patients[54] and as first-line therapy in older women with metastatic breast cancer.[55] In a trial involving 43 anthracycline-pretreated patients, capecitabine achieved a response rate of 36% [95% confidence (CI) 17–59%] including complete responses in 14% of patients, whereas the response rate with paclitaxel was 26% (95% CI 9–51%) with no complete responses.[54] Overall survival and time to disease progression were similar in the two treatment groups. In the second study in 95 patients, which investigated the efficacy and safety of capecitabine in patients aged $\geqslant$55 years or older, the response rate was 30% (95% CI 19–43%) with capecitabine. The response rate in patients receiving CMF was 16% (95% CI 5–33%).[55] The median overall survival was 19.6 months with capecitabine and 17.2 months with CMF.

Safety data from these four phase II trials indicate that capecitabine is generally well tolerated, with a safety profile typical of infused fluoropyrimidines. The most frequent treatment-related adverse events were gastrointestinal effects (diarrhea, nausea and vomiting) and the cutaneous side effect hand–foot syndrome. Alopecia and myelosuppression were rare in all trials. Most adverse events were mild to moderate in intensity and the only grade 3/4 adverse events to occur in more than 10% of patients were diarrhea (12%) and hand–foot syndrome (grade 3: 13%; grade 4: not applicable). All adverse events could be managed by treatment interruption and, if necessary, dose reduction without compromising efficacy.[56]

Colorectal cancer

Capecitabine has also shown considerable promise in the treatment of colorectal cancer. Two large, randomized phase III trials have compared capecitabine with i.v. 5-FU/leucovorin (Mayo Clinic regimen) as first-line therapy for metastatic colorectal cancer. Patients were randomized to treatment with either capecitabine (1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period) or Mayo Clinic regimen (20 mg/m^2 leucovorin followed by 425 mg/m^2 5-FU, administered as an i.v. bolus on days 1–5 every 28 days). The results of the two studies demonstrated that capecitabine is at least as effective as i.v. bolus 5-FU/leucovorin, with a significantly superior response rate and equivalent survival and time to disease progression.[57,58] A prospectively planned analysis of the pooled data from the two trials (1207 patients) confirmed these results, with significantly superior response rates (26 versus 17%, $p<0.0002$) and equivalent overall survival (median 12.9 versus 12.8 months) (Figure 2) and time to disease progression (median 4.6 versus 4.7 months) compared with i.v. bolus 5-FU/leucovorin.[59] The safety profile of capecitabine was superior to that observed with 5-FU/leucovorin, with a significantly lower incidence of diarrhea, stomatitis, nausea and alopecia. Hand–foot syndrome was more common with capecitabine, but was effectively managed by treatment interruption and individual dose titration, if appropriate, without loss of efficacy.[60]

The results from these studies in metastatic breast and colorectal cancer indicate that capecitabine is at least as effective as current therapies with additional benefits in safety and convenience for patients.

Future directions with capecitabine

The majority of capecitabine clinical trials have been conducted in patients with breast and colorectal cancer, where capecitabine has shown considerable promise. However, more recently, capecitabine monotherapy has been investigated in other tumor types, including pancreatic, ovarian, and head and neck cancers.[61,62] In addition, several combination regimens including capecitabine have been evaluated in phase I/II trials and appear promising. These include capeci-

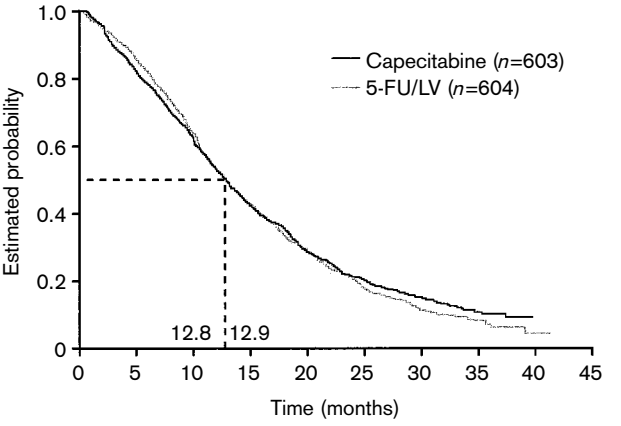

Figure 2. Overall survival, capecitabine versus 5-FU/leucovorin.

tabine plus irinotecan or oxaliplatin in colorectal cancer,[63,64] capecitabine plus radiotherapy in rectal cancer,[65] capecitabine plus paclitaxel or docetaxel in breast cancer,[66–68] capecitabine plus epirubicin/docetaxel in breast cancer[69] and capecitabine plus gemcitabine in pancreatic cancer.[70]

Conclusion

5-FU has long been used to treat a variety of solid tumors and will undoubtedly continue to play a role in cancer therapy. However, its use is limited by the need for i.v. administration, dose-limiting toxicities and the development of resistance. Many attempts have been made to maximize its efficacy and minimize the adverse effects associated with 5-FU, including the use of protracted, intermittent and chronomodulated i.v. schedules, and combination with other cytotoxic agents and biomodulators, most notably leucovorin.

At present, triple-drug regimens including 5-FU are commonly used in first-line therapy of breast cancer and new, more convenient methods of administering 5-FU provide attractive alternatives to current treatment regimens. In addition, treatment of patients resistant to anthracyclines and taxoids is becoming an increasingly common problem as more active agents, including taxanes, are used earlier in treatment or as adjuvant therapy.

In these contexts, novel, effective, oral agents are attracting widespread interest. Capecitabine is a novel, oral fluoropyrimidine carbamate that generates 5-FU preferentially within tumors. Tumor selectivity is achieved through exploitation of the high intratumoral concentrations of the enzyme TP, which governs the last stage in the conversion of capecitabine to 5-FU. This results in generation of 5-FU preferentially in tumor tissues. Capecitabine has demonstrated high activity and a favorable safety profile in a range of settings in breast and colorectal cancer therapy. Furthermore, the low incidence of myelosuppression seen with capecitabine makes it an ideal agent for combination therapy in both first- and second-line treatment regimens. The use of capecitabine instead of i.v. 5-FU in combination regimens may enable further improvements in response rates, time to disease progression and possibly survival. In addition, oral therapy is likely to have beneficial cost implications, encouraging home-based management and reducing nursing and day-care costs. Most importantly, oral therapy provides considerable benefits to patients in terms of quality of life and convenience, which is of particular importance in the palliative setting. As results of ongoing trials of capecitabine as a component of combination regimens become available, the potential of this novel, tumor-selective agent is likely to become clearer.

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