Vision of the Future: Capecitabine

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ABSTRACT

Capecitabine is a thymidine phosphorylase (TP)-activated oral fluoropyrimidine, rationally designed to generate 5-fluorouracil (5-FU) preferentially within tumors. This tumor selectivity is achieved through exploitation of the significantly higher activity of TP in tumor compared with healthy tissue. The high single-agent activity of capecitabine in breast and colorectal cancer suggests that capecitabine may have a role in the treatment of other tumor types that are sensitive to 5-FU, such as pancreatic cancer. Tumor types known to have a high level of TP activity, such as renal cancer, are especially attractive targets for capecitabine therapy. Capecitabine has potential as monotherapy in these tumor types, or as a combination partner for other cytotoxic agents with different mechanisms of action and little overlap of key toxicities. In particular, some cytotoxic drugs, such as the taxanes and cyclophosphamide, are known to upregulate TP activity in tumor tissue, offering the potential for synergistic action. The combination of capecitabine and docetaxel has demonstrated significant activity in women with anthracycline-pretreated breast cancer, and is the only cytotoxic combination to significantly increase survival compared with standard therapy in this setting. In addition, capecitabine as monotherapy or in combination with other cytotoxic agents has shown encouraging activity in pancreatic, ovarian, and renal cell cancers. This article discusses recent data from clinical trials investigating capecitabine in a range of tumor types, highlighting the potential future role of capecitabine as an alternative to traditional i.v. chemotherapy. The Oncologist 2001;6(suppl 4):35-39

INTRODUCTION

Capecitabine, a thymidine phosphorylase (TP)-activated fluoropyrimidine, was rationally designed to generate 5-fluorouracil (5-FU) preferentially at the tumor site. This tumor selectivity is achieved through exploitation of the significantly higher activity of TP in tumor tissue compared with healthy tissue [1]. Because capecitabine mimics continuous-infusion 5-FU and has demonstrated considerable activity in breast and colorectal cancer, it has attracted interest as treatment for other tumor types known to be sensitive to 5-FU or in which TP is upregulated. Capecitabine potentially offers a more convenient alternative to i.v. 5-FU therapy in numerous tumor types commonly treated with 5-FU. Therefore, clinical trials are investigating the role of capecitabine as treatment for cancers of the stomach, pancreas, esophagus, head and neck, ovary, cervix, kidneys, prostate, liver, and biliary tract, as well as endocrine tumors and mesothelioma.

CAPECITABINE IN BREAST CANCER

Capecitabine has demonstrated high single-agent activity in patients with metastatic breast cancer whose disease has progressed during or following anthracycline- and taxane-based therapy. A large, multicenter phase II trial in 163 patients with anthracycline- and paclitaxel-pretreated metastatic breast cancer showed that capecitabine achieves a response rate of 20%, with an impressive 29% response rate in a retrospectively defined subpopulation of patients refractory to both paclitaxel and doxorubicin [2]. Median overall survival was 12.6 months. In addition, capecitabine therapy was associated with symptom relief and a favorable safety profile. These results with heavily pre-treated patients indicate that capecitabine has potential as a convenient, active, and well-tolerated treatment option earlier in the disease course or as a combination partner for standard cytotoxic agents. Agents that
upregulate TP activity, such as the taxanes, mitomycin C, and cyclophosphamide, are particularly attractive combination partners, potentially offering synergy with capecitabine (Fig. 1) [3]. Of these agents, docetaxel has been investigated most extensively as a combination partner for capecitabine. Both capecitabine and docetaxel have considerable single-agent activity in patients with metastatic breast cancer, distinct mechanisms of action, and only partial overlap of key toxicities. A phase I study in patients with solid tumors identified two feasible regimens of capecitabine plus docetaxel: capecitabine 1,250 mg/m² in combination with docetaxel 75 mg/m², and capecitabine 825 mg/m² twice daily plus docetaxel 100 mg/m² [4]. The former was selected for further evaluation in a randomized, phase III trial, on the basis that docetaxel 75 mg/m² is the standard dose in combination regimens, and has demonstrated single-agent activity. A total of 511 patients with anthracycline-pretreated advanced breast cancer were randomized to 21-day cycles of either capecitabine 1,250 mg/m² twice daily on days 1-14 plus docetaxel 75 mg/m² on day 1, or docetaxel 100 mg/m² on day 1 [5]. Patients with a tumor response or stable disease after 6 weeks of treatment continued on study therapy until disease progression or unacceptable toxicity.

The combination of capecitabine with docetaxel offered significantly superior efficacy compared with docetaxel monotherapy. Progression-free survival, the primary endpoint, was significantly superior with the combination regimen (hazard ratio = 0.64, p = 0.0001). This means that the risk of disease progression was reduced by 36% in patients receiving the combination regimen. Median progression-free survival was 6.1 months with capecitabine/docetaxel combination therapy compared with 4.2 months in the monotherapy arm. Moreover, the combination regimen resulted in a significantly superior overall survival (hazard ratio = 0.75, p = 0.0119), with risk of death reduced by 25% in patients receiving combination therapy. The median overall survival was 13.7 months with combination therapy and 11.1 months with monotherapy.

Compared with monotherapy, combination treatment was associated with increased incidences of gastrointestinal side effects and hand-foot syndrome, whereas pyrexia, myalgia, arthralgia, and neutropenic fever were more common in the monotherapy arm. Adverse events were manageable with appropriate medical intervention, treatment interruption, and, if necessary, dose adjustment. Of note, there was no significant difference in quality of life in the two treatment arms. In addition, the incidence of hospitalizations due to treatment-related adverse events was similar in the two treatment arms.

Ongoing and planned trials are currently investigating a number of different schedules and dose regimens of capecitabine/docetaxel combination therapy,
including weekly docetaxel, docetaxel administered on day 8, and capecitabine administered at a twice-daily dose of 1,000 mg/m² for 14 days followed by a 7-day rest period. The rationale for administering docetaxel on day 8 of each 21-day cycle (i.e., in the middle of capecitabine treatment) was provided by a preclinical study in which this schedule resulted in more pronounced synergy compared with administration of docetaxel on day 1 or 15 [6].

Capecitabine is also being evaluated as a combination partner for paclitaxel, vinorelbine, cyclophosphamide/epirubicin, and epirubicin/docetaxel, and as a component of all-oral regimens (with idarubicin and cyclophosphamide). Cyclophosphamide is of particular interest, as it has been shown to upregulate TP expression in tumor tissue [7]. Results of several phase I and II trials suggest that capecitabine may play a valuable role in a variety of combination regimens used in the treatment of breast cancer, and further evaluation is ongoing.

CAPECITABINE IN PANCREATIC CANCER

Pancreatic cancer is usually poorly responsive to chemotherapy, and is typically treated with gemcitabine and/or 5-FU (as single agents or in combination). However, confirmed response rates are usually less than 10% and median survival is typically 3-5 months in previously untreated patients. Because pancreatic cancer is sensitive to 5-FU, and TP activity is significantly higher in pancreatic tumor tissue than in adjacent normal tissue, TP-activated capecitabine is a promising therapy in this setting.

In a phase II trial investigating the safety and efficacy of capecitabine, 42 patients with advanced or metastatic pancreatic cancer received standard capecitabine monotherapy (1,250 mg/m² twice daily on days 1-14 of a 21-day cycle) [8]. The safety profile of capecitabine was similar to that observed with capecitabine in colorectal and breast cancer: predominant grade 3/4 adverse events were diarrhea, hand-foot syndrome, and nausea. There were three confirmed partial responses (7%) and a further 17 patients (41%) achieved stable disease as their best response (including disease stabilization for ≥12 weeks in 11 patients [26%]). The median duration of response was 2.8 months and the median overall survival was a favorable 6.0 months. Capecitabine therapy also provided symptomatic relief: 10 patients (24%) achieved a positive Clinical Benefit Response score, with a further 16 patients (38%) achieving a stable score. In addition, pain intensity was stabilized in 25 patients (60%) and reduced in a further 12 patients (29%).

Another phase II trial has investigated capecitabine in combination with gemcitabine in pancreatic cancer. Gemcitabine has demonstrated modest activity in pancreatic cancer, and in a phase II trial, gemcitabine in combination with continuous-infusion 5-FU resulted in a 20% response rate in patients with previously untreated pancreatic cancer [9]. Several factors suggested that capecitabine in combination with gemcitabine may offer similar or enhanced efficacy with a more favorable safety profile. Capecitabine mimics continuous-infusion 5-FU, has demonstrated single-agent activity in pancreatic cancer, and has a toxicity profile that differs from that of gemcitabine. In addition, in preclinical models, gemcitabine was shown to upregulate TP and was synergistic with capecitabine [10]. Therefore, a phase I, dose-finding trial was conducted to investigate intermittent capecitabine in combination with gemcitabine in 27 patients with previously untreated pancreatic cancer [11].

Capecitabine was administered at escalating doses, with i.v. gemcitabine at a fixed dose of 1,000 mg/m² on days 1 and 8. The dose-limiting toxicities were neutropenia and mucositis. A 21-day regimen of capecitabine 650 mg/m² twice daily on days 1-14 in combination with gemcitabine 1,000 mg/m² on days 1 and 8 was identified as the most appropriate regimen for further evaluation. There was only one grade 4 adverse event in the 12 patients treated at this dose level, and there were no cases of diarrhea, hand-foot syndrome, or alopecia in these patients. The overall response rate in all patients with evaluable disease was 29%. The recommended regimen identified in this trial will be compared with gemcitabine monotherapy in a randomized, phase III trial.

CAPECITABINE IN OVARIAN CANCER

There is also a clinical need for new treatments for patients with ovarian cancer. Capecitabine (1,250 mg/m² twice daily on days 1-14 of a 21-day cycle) has shown encouraging activity as a novel monotherapy for patients with taxane and platinum pretreated ovarian cancer. In a phase II trial, 6 (32%) of 19 evaluable heavily pretreated patients (who had previously received platinum compounds and taxanes) achieved a CA-125 response according to the strict Rustin criteria [12], defined as a 50% or 75% reduction in CA-125 concentration maintained over three or four serial evaluations, respectively [13]. In addition, a further eight patients achieving stable or decreased (by >50%) serum concentrations of CA-125 lasting for at least six treatment cycles and two of nine patients (22%) with measurable disease achieved a radiologically confirmed response (one complete and one partial response). Further studies are warranted to investigate capecitabine as a component of first-line combination regimens (e.g., with platinum compounds or taxanes) or as...
an alternative to more toxic, i.v. regimens in the palliative setting.

CAPECITABINE IN RENAL CANCER

In preclinical studies, renal cell tumors demonstrated high TP activity, suggesting that TP-activated capecitabine may be effective in this setting. In a pilot phase II study, capecitabine (1,250 mg/m² twice daily for 14 days followed by a 7-day rest period) was administered to 22 patients with metastatic renal cell cancer that had progressed during or following immunotherapy [14]. Among 12 patients for whom efficacy and toxicity data have been reported, one patient achieved a partial response, and disease was stabilized in all but one of the remaining patients (83%). There were no grade 4 adverse events and the only grade 3 adverse event was hand-foot syndrome, which occurred in two patients and resolved without capecitabine dose modification. Another phase II study has investigated capecitabine (1,000 mg/m² twice daily on days 1-5 of weeks 5-8) in combination with immunotherapy (interleukin 2, interferon-α, and oral 13-cis-retinoic acid) in 30 patients with metastatic renal cell carcinoma [15]. This regimen, repeated for up to three cycles, produced an objective response rate of 34%, including two complete responses. A further 12 patients (40%) achieved disease stabilization. No grade 4 adverse events were observed, and grade 3 events were reported in only two patients (malaise and malaise, nausea/vomiting). A randomized, phase III trial has been initiated to further investigate the activity and tolerability of capecitabine in combination with immunotherapy in patients with renal cell cancer.

CONCLUSIONS

Oral capecitabine has considerable single-agent activity in metastatic breast and colorectal cancer and has demonstrated a favorable tolerability profile, with a notably low incidence of myelosuppression. The crucial role of TP in the activation of capecitabine provides a strong preclinical rationale for evaluating capecitabine in combination with agents that upregulate TP in tumor tissues, such as the taxanes, cyclophosphamide, gemcitabine, and vinorelbine [3]. Consequently, a number of novel, rationally designed combination regimens are being explored. In a randomized, phase III trial, capecitabine plus docetaxel combination therapy resulted in significantly higher tumor response rates, time to disease progression, and overall survival compared to docetaxel alone, with a manageable safety profile.

Capecitabine has also shown promising activity in other tumor types sensitive to 5-FU, especially those known to exhibit high intratumoral TP activity, such as pancreatic, ovarian, and renal cell cancers. In the future, capecitabine may replace i.v. 5-FU in many clinical settings, providing patients with a more convenient and potentially more effective, better-tolerated treatment option.

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