Cytotoxicity and genotoxicity of capecitabine in head and neck cancer and normal cells

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Abstract The interaction between a chemical and a cell may strongly depend on whether this cell is normal or pathological. Side effects of anticancer drugs may sometimes overcome their benefit action, so it is important to investigate their effect in both the target and normal cells. Capecitabine (Xeloda, CAP), a prodrug of 5-fluorouracil, is mainly used in colorectal cancer, but little is known about its action in head and neck cancer. We compared the cytotoxic and genotoxicity of CAP in head and neck HTB-43 cells and normal human lymphocytes by comet assay and flow cytometry. CAP at concentration up to 50 μM significantly decreased the viability of the cancer cells, whereas it did not affect normal lymphocytes. The drug did not interact with isolated plasmid DNA, but it damaged DNA in both cancer and normal cells. However, the extent of the damage in the former was much higher than in the latter. CAP induced apoptosis in the cancer cells, but not in normal lymphocytes. Pre-treatment of the cells with the nitrone spin traps 2-((4-pyridil-1-oxide)-N-tert-butyl-nitroxide and N-tert-butyl-2-phenyl-nitroxide decreased the extent of CAP induced DNA damage, suggesting that free radicals may be involved in the formation of DNA lesions induced by CAP. The drug evoked an increase in the G0/G1 cell population accompanied by a decrease in the S cell population. CAP may evoke a pronounced cyto- and genotoxic effects in head and neck cancer cells, whereas it may or may not induce such effects in normal cells to far lesser extent.

Keywords Capecitabine · Head and neck cancer · DNA damage · DNA repair · Apoptosis · Cell cycle

Introduction

Chemotherapy in head and neck cancer is a multi-stages process, in which 5-fluorouracil (5-FU), a fluorinated analog of uracil, plays a pivotal role [1, 2]. This drug displays activity in various regimes of therapy of squamous cell carcinoma of the head and neck (HNSCC) and its combination with cisplatin and radiation improves the efficacy of the treatment. After entering the cell, 5-FU is metabolized in a rather complex way, including at least four pathways, one of which gives rise to 5-FUTP [3]. Because the atom of fluorine is similar in size to hydrogen in UTP, DNA polymers include 5-FU in all classes of RNA, 5-FU may also produce 5-FdUMP, which is an inhibitor of thymidylate synthase (TS), involved in the synthesis of DNA. TS inhibiting results in blocking of formation of dTMP and, therefore, decreasing the availability of dTTP for DNA replication and repair. Cytotoxic effect of 5-FU can also be mediated by its incorporation into DNA and changes in some membrane function in cancer cells treated with the drug [4]. The use of 5-FU has several limitations. The activity of the drug is limited by its rapid degradation by the cytosolic enzyme dihydropyrimidine dehydrogenase,
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References

Clinical Efficacy of Capecitabine and Cyclophosphamide (XC) in Patients with Metastatic Breast Cancer

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Combined low-dose therapy of oral capecitabine (Xeloda) and cyclophosphamide (XC) has been demonstrated to be useful for long-term control of lesions in patients with metastatic breast cancer (MBC) and is aimed at symptomatic alleviation and prolongation of survival. Here, a retrospective review was conducted of MBC patients administered XC at the Okayama University Hospital (OUH), to evaluate responses to XC, adverse events and time to progression (TTP). Twenty patients with MBC received XC between 2006 and 2009. With the exception of 2 elderly patients who were over the age of 70 at the initial examination, all of the patients had received prior treatment with an anthracycline and/or a taxane. No complete response (CR) cases were observed, but partial response (PR) was achieved in 6 patients (30%) and SD in 9 (45%), of whom 5 (20%) sustained SD status for ≥12 months. The median TTP was 6 months (range: 3–27 mo.). Three patients developed Grade 3 adverse events (diarrhea, nausea and stomatitis), but no other patients developed adverse reactions causing interruption of the therapy. XC was safe even in previously treated and elderly MBC patients; moreover, it yielded remarkable clinical responses.

Key words: metastatic breast cancer, metronomic, chemotherapy

With advances in the development of new drugs in recent years, an expanded repertoire of pharmacotherapeutic strategies has become available for breast cancer. As molecular-targeting drugs become more widespread, pharmacotherapy has become increasingly more effective but also more complex. The selection of drugs must be based on results of individual drug sensitivity assessments. In the case of breast cancer treatment, in particular, the most suitable therapeutic regimens should be selected not only based on assessment of the indication for hormone therapy or for the molecular-targeting drug trastuzumab by determining the estrogen receptor (ER) and HER2 expression status, but also by taking into account the tumor characteristics, such as the malignancy grade, extent of lymph node metastasis, and sites of distant metastasis through translational research which has been applied extensively in recent years. Risk factors such as adverse reactions, cost, and the social environment of the patients are also of importance in this determination. In particular, treatment for recurrent carcinoma of the breast is still aimed primarily at prolongation of survival and alleviation of symptoms rather than at cure of the malignancy, so that the weight of each of these factors diverges widely from that during the consideration of adjuvant chemotherapy, which is aimed at cure. It sum, theoretical and clinical evidence-based evaluation

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X-Ray Irradiation Induces Thymidine Phosphorylase and Enhances the Efficacy of Capecitabine (Xeloda) in Human Cancer Xenografts

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ABSTRACT

Thymidine phosphorylase (dThdPase) is an essential enzyme for the activation of the cytosstatics capecitabine (5'-deoxy-5-fluorouridine) and its intermediate metabolite 5'-deoxy-5-fluorouracil (5'-dFUrd) to 5-fluorouracil (5-FUra) in tumors. We observed previously that several cytokines and cytosstatics up-regulated dThdPase expression and consequently enhanced the efficacy of capecitabine and 5'-dFUr. In the present study, we found that X-ray irradiation also up-regulated dThdPase expression in several human cancer xenografts. A single-dose local irradiation at 5 Gy increased dThdPase levels by up to 13-fold at 9 days after the irradiation. Whole-body irradiation also up-regulated dThdPase in a tumor, but it did not increase the enzyme level in the liver. We also observed that the irradiation increased the levels of human tumor necrosis factor α (TNF-α), which is an up-regulator of dThdPase, prior to the dThdPase up-regulation. These results indicate that X-ray irradiation might increase dThdPase levels indirectly through the human TNF-α in the tumor tissue. In the WiDr colon and MX-1 mammary human cancer xenograft models, the combination of a single local X-ray irradiation with either capecitabine or 5'-dFUr was much more effective than either radiation or chemotherapy alone. In contrast, treatment with X-ray irradiation and 5'-FUr in combination showed no clear additive effects. Combined modality treatment of cancer patients with capcitabine and X-ray irradiation would have greater potential usefulness than conventional radiochemotherapy with 5-FUra.

INTRODUCTION

Capecitabine is a novel fluoropyrimidine carbamate that is being used clinically for the treatment of breast cancer patients who have failed paclitaxel and anthracycline regimens (1), and it is being assessed for the treatment of other types of cancer. It generates the active drug 5-FUra selectively in tumors by three enzymes located in the liver and in tumors; the final step is the conversion of the intermediate metabolite 5'-dFUr to 5-FUra by dThdPase in tumors (2, 3). This conversion appeared to be a rate-limiting step for the efficacy of capcitabine. We observed that the conversion was insufficient in a human cancer xenograft line, which was refractory to capcitabine in vivo therapy (4), and that the susceptibility of human cancer xenografts to 5'-dFUr correlated with their levels of dThdPase expression (5). Therefore, the efficacy of capcitabine and its intermediate 5'-dFUr would be optimized by selecting patients who have tumors with high levels of dThdPase expression. Another useful approach for optimizing capcitabine and 5'-dFUr therapy would be a combination therapy with their rational partners, such as up-regulators of dThdPase.

Previously, we reported that several cytokines, such as IL-1α, TNF-α, IFN-γ, up-regulated dThdPase mRNA expression in human cancer cells and increased the susceptibility of the tumor cells to 5'-dFUr (6). Furthermore, we observed in human cancer xenograft models that the anticancer drugs, such as paclitaxel and docetaxel, increased tumor levels of dThdPase expression and consequently showed a synergistic anticancer activity with capcitabine (7). We suggested that the taxanes might increase dThdPase level indirectly through the up-regulation of TNF-α, because the taxanes simultaneously increased tumor levels of human TNF-α. Several factors have been reported to up-regulate TNF-α. It is, therefore, of interest to investigate whether factors other than taxanes increase dThdPase levels in tumors and make the tumors more susceptible to capcitabine. In the present study, we found that X-ray irradiation, which is known to up-regulate TNF-α (8–10), indeed increased tumor levels of both TNF-α and dThdPase. Consequently, the efficacy of X-ray irradiation and either capcitabine or 5'-dFUr in combination was much better than either treatment in human cancer xenograft models. We describe these results and discuss the potential of this rational combination therapy for cancer patients with either capcitabine or 5'-dFUr and X-ray irradiation.

MATERIALS AND METHODS

Chemicals. Capecitabine and its intermediate metabolite 5'-dFUr were obtained from F. Hoffmann-La Roche (Basle, Switzerland). 5-FUra was purchased from Kyowa Hakko Co. (Tokyo, Japan). 2.2'-Anhydro-5-ethyluridine was synthesized by the method described elsewhere (11).

Capecitabine and 5'-dFUr were dissolved or suspended in 40 mM citrate buffer (pH 6.0) containing 5% gum arabin as the
Comparison of pharmacokinetics and safety profiles of two capecitabine tablet formulations in patients with colon, colorectal or breast cancer

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Abstract

Purpose The objective of this study was to compare the pharmacokinetics and safety of two tablet formulations containing 500 mg of capecitabine (CAS number 154361-50-9) in patients with colon, colorectal or breast cancer.

Methods The study was a multicentric, open label, randomized, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study in patients of either sex with colon, colorectal or breast cancer. Eligible patients received each treatment in a crossover manner under fed conditions according to the randomization schedule. The pre-dose blood sample was taken within 90 min prior to dosing, and serial blood sampling was done up to 10.00 h post-dose under monochromatic light. The analysis of plasma samples for concentrations of capecitabine and 5′-deoxy-5-fluorocytidine (5′-DFCR) was carried out using a validated liquid chromatography mass spectrometry method. Bioequivalence was to be concluded if the confidence intervals so constructed were within the range of 80–125 % for \( C_{\text{max}} \), \( \text{AUC}_{0-\text{t}} \), and \( \text{AUC}_{0-\text{t}} \) of capecitabine and 5′-DFCR. Patients were monitored for safety and tolerability throughout the study.

Results The 90 % confidence intervals for the “test/reference” mean ratios of the ln-transformed pharmacokinetic variables \( C_{\text{max}} \), \( \text{AUC}_{0-\text{t}} \), and \( \text{AUC}_{0-\text{t}} \) were clearly within the conventional bioequivalence range of 80–125 %. Both the formulations were reasonably tolerated after a single oral dose in patients.

Conclusions Both the capecitabine tablet formulations demonstrated equivalent rate and extent of systemic absorption, and hence were considered bioequivalent. Therefore, the two formulations can be considered as equivalent in terms of pharmacokinetics and safety profiles.

Keywords Capecitabine · Bioequivalence · Pharmacokinetics · Safety

Introduction

As per the WHO fact sheet No.297 October 2011, cancer is the leading cause of death worldwide [1]. Colorectal cancer and breast cancer are amongst the main types of cancer, and the medical management is treatment with chemotherapeutic agents such as 5-fluorouracil (5-FU). 5-FU, introduced over five decades ago, has remained a mainstay in treatment regimens for colorectal cancer (CRC) since that time, both alone and in combination with other agents. However, its short half-life, requirement for a central line and the need for continuous infusions led researchers to design an oral formulation of the drug. In June 2005, this oral drug, capecitabine (CAS number 154361-50-9), was approved by the Food and Drug Administration (FDA) as a first-line therapy in patients with metastatic colorectal cancer when single-agent fluoropyrimidine is preferred [2]. The drug is also approved for use as a single agent in metastatic breast cancer patients who are resistant to both anthracycline and paclitaxel-based regimens or when further anthracycline treatment is contraindicated. It is also approved in combination with docetaxel after failure of
In-transformed pharmacokinetic variables $C_{max}$, $AUC_{0-\infty}$ and $AUC_{0-\infty}$ (as primary characteristics of the extent of absorption of capcitabine and 5'-DFCR) were within the conventional bioequivalence range of 80–125%. Both the formulations of capcitabine 500 mg tablets were reasonably tolerated after a single oral dose in patients with colon, colorectal or breast cancer.

Significant cancer treatment costs may severely compromise the medical management of the suffering individual, especially in the developing countries. In such a case, therapeutically equivalent formulation at an affordable cost may enhance the patient compliance to the treatment regimen.

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Conflict of interest No author of this proposed publication has financial disclosure or conflict interest in the subject matter discussed in this manuscript.

References

1. WHO fact sheet N°297 October 2011
Pharmacokinetic evaluation of capecitabine in breast cancer

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Introduction: Capecitabine, an oral prodrug of 5-fluorouracil (5-FU), is adsorbed in its intact form through the intestine and metabolized to 5-FU in tumour cells. In metastatic breast cancer (MBC), capecitabine is an effective and well-tolerated therapeutic option both in monotherapy and in combination with chemotherapeutic or molecular-targeted agents.

Areas covered: We summarized data on pharmacokinetics and pharmacodynamics of capecitabine. We also produced a general review of the most relevant clinical studies of capecitabine in MBC. A literature search was performed using PubMed database including selected articles published in English language up to October 2012.

Expert opinion: The unique pharmacodynamic/pharmacokinetic features represent the bases of the reduced toxicity and the activity of capecitabine in several tumours. Although during the past 10 years there has been an increasing use of this drug in MBC both as single agent and in combination, encouraging results of well tolerated and active combinations with novel agents will lead to a more extensive and protracted use of capecitabine. In view of this, some aspects should be further clarified such as the optimal starting dose and the introduction of alternative schedules of treatment.

Keywords: 5-fluorouracil, breast cancer, capecitabine, pharmacokinetics


1. Introduction

Capecitabine was developed as oral prodrg of 5-fluorouracil (5-FU), a fluoropyrimidine used from more than 50 years for the treatment of the most common solid tumours, including breast cancer (BC).

5-FU acts through inhibition of the enzyme thymidylate synthase (TS) and the incorporation of its metabolites into RNA and DNA. 5-FU in combination with other chemotherapeutic agents improved overall response rate (ORR) and survival in breast, colorectal and head and neck cancers [1].

5-FU is administered intravenously, due to its unpredictable gastrointestinal absorption. In addition, the relatively short plasma elimination half-life (10 – 20 min) limits its activity. These features make the 5-FU administration particularly complicated since it is essentially through close boluses or, as preferred, continuous infusion [2]. Moreover, the treatment with 5-FU is associated with serious side effects, such as gastrointestinal toxicity and myelosuppression.

To overcome these disadvantages, oral pro-drugs of 5-FU were developed (i.e., capecitabine, tegafur and 5’-deoxy-5-fluorouridine, 5’-DFUR). In this review, we summarize the pharmacodynamic and pharmacokinetic profile of capecitabine, particularly focusing our attention on BC.


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Capcitabine Monotherapy: Safe and Effective Treatment for Metastatic Breast Cancer

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Key Words. Capcitabine • Breast cancer • Single agent • Monotherapy • Efficacy • Safety • Quality of life

LEARNING OBJECTIVES
After completing this course, the reader will be able to:
1. Describe the pharmacology of capcitabine.
2. Discuss the use of capcitabine as a single agent and in refractory disease.
3. Discuss safety and dosing considerations.
4. Describe current adjuvant treatment with capcitabine.

ABSTRACT
Optimal management for metastatic breast cancer frequently involves cytotoxic chemotherapy. Over the years, several complex multidrug regimens have been developed that were based upon a rationale of synergistic antitumor activity and nonoverlapping toxicities. However, recently the clinical value of these complex regimens has been called into question as several drugs used alone (monotherapy) or in sequence (serial single agent) have been shown to be both efficacious and better tolerated. Capcitabine (an orally administered fluoropyrimidine carbamate) is one such agent that has been proven to be effective when used alone for metastatic breast cancer, metastatic colorectal cancer, and adjuvant colon cancer. In this review, published (or reported in abstract form) data examining various aspects of clinical response and tolerability with single-agent capcitabine for (primarily) first- and second-line metastatic breast cancer are examined. For the most part, response rates are comparable with those of the more complex regimens. Dose reductions from the labeled dose of 1,250 mg/m² twice daily are relatively common. Toxicities (following dose reductions if needed) are generally manageable, even by more frail patients. Elderly patients are more likely to have impaired renal function or be receiving warfarin treatment, and special attention to these factors is warranted. Nonetheless, the drug administered alone is a reasonable choice when single-agent chemotherapy is entertained as a treatment option for metastatic breast cancer, including in the first-line setting. The Oncologist 2006;11:325–335

INTRODUCTION
Breast cancer is the most frequently diagnosed cancer in women and the second leading cause of cancer-related deaths (following lung cancer), with 212,930 new cases and 40,870 cancer-related deaths projected for 2005 [1]. Five-year survival rates decrease with advancing disease stage.

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83 Yamamoto T, Inoue S, Kilamser K et al. Multicenter phase II study of trastuzumab (H) and capecitabine (X) as first- or second-line treatment in HER2 over-expressing metastatic breast cancer (Japan Breast Cancer Study Group: JBCSG-003). J Clin Oncol 2005;23:78s.

Randomised, phase II trial comparing oral capecitabine (Xeloda$^R$) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines

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Capecitabine, an oral fluoropyrimidine carbamate, was designed to generate 5-fluorouracil preferentially at the tumour site. This randomised, phase II trial evaluated the efficacy and safety of capecitabine or paclitaxel in patients with anthracycline-pretreated metastatic breast cancer. Outpatients with locally advanced and/or metastatic breast cancer whose disease was unresponsive or resistant to anthracycline therapy were randomised to 3-week cycles of intermittent oral capecitabine (1255 mg m$^{-2}$ twice daily, days 1–14, (22 patients)) or a reference arm of i.v. paclitaxel (175 mg m$^{-2}$, (20 patients)). Two additional patients were initially randomised to continuous capecitabine 666 mg m$^{-2}$ twice daily, but this arm was closed following selection of the intermittent schedule for further development. Overall response rate was 36% (95% CI 17–59%) with capecitabine (including three complete responses) and 26% (95% CI 9–51%) with paclitaxel (no complete responses). Median time to disease progression was similar in the two treatment groups (3.0 months with capecitabine, 3.1 months with paclitaxel), as was overall survival (7.6 and 9.4 months, respectively). Paclitaxel was associated with more alopecia, peripheral neuropathy, myalgia and neutropenia, whereas typical capecitabine-related adverse events were diarrhoea, vomiting and hand–foot syndrome. Twenty-three per cent of capecitabine-treated patients and 16% of paclitaxel-treated patients achieved a $\geq$10% improvement in Karnofsky Performance Status. Oral capecitabine is active in anthracycline-pretreated advanced/metastatic breast cancer and has a favourable safety profile. Furthermore, capecitabine provides a convenient, patient-oriented therapy.


Keywords: anthracycline-resistant; breast cancer; capecitabine; fluoropyrimidine; paclitaxel

Every year more than 425 000 women in Europe and the USA are diagnosed with breast cancer (Black et al, 1997; Landis et al, 1999), nearly half of whom will develop metastatic disease (Lippman, 1998). The prognosis for women with metastatic and/or advanced disease is poor, with a mean survival time of approximately 18 to 30 months from diagnosis (Perez, 1998). In these circumstances, the primary goal of therapy is palliation (Hortobagyi, 1996; Blum, 1999; Parfitt, 1999) and treatment usually involves hormonal therapy or chemotherapeutic agents (Hortobagyi, 1998; Marty et al, 1999).

The widespread use of anthracycline-containing regimens as adjuvant and first-line treatment for breast cancer has resulted in an increase in the number of patients presenting with disease that is resistant to anthracyclines (Marty et al, 1999). The use of M-phase inhibitors such as taxanes and vinorelbine in these patients is widely accepted. Response rates of 22 to 28% are reported for paclitaxel (Perez, 1998), 29 to 41% for docetaxel (Bonnetterre et al, 1999; Trudel, 1999) and 15 to 16% for vinorelbine in this setting (Degardin et al, 1994; Ibrahim et al, 1999). The duration of remission is approximately 4 to 5 months (Degardin et al, 1994; Ibrahim et al, 1999).

Capecitabine (Xeloda$^R$) is a tumour-selective fluoropyrimidine carbamate designed to mimic continuous infusion 5-FU and to generate 5-FU preferentially in tumour tissue by exploiting the higher concentrations of thymidine phosphorylase (TP) found in malignant cells compared with normal cells (Miwa et al, 1998). Following oral administration, capecitabine passes intact through the intestinal mucosa and is rapidly and extensively metabolised via a sequential triple enzyme pathway. Capecitabine and its intermediate metabolites are not cytotoxic, and require conversion to 5-FU by TP. Moreover, since elevated TP concentrations correlate with a poor prognosis in breast cancer patients (Toi et al, 1997), capecitabine may be particularly effective in this group of patients (Frings, 1998).

The selective tumour activation of capecitabine has been confirmed in a trial of patients with colorectal cancer (Schüller et
Capecitabine vs paclitaxel in metastatic advanced breast cancer
DC Tabot et al

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Capecitabine-based chemotherapy for metastatic colorectal cancer

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Abstract
Purpose Metastatic colorectal cancer (MCRC) remains a significant public health concern. The objectives of present study are to investigate the efficacy and safety profile of capecitabine-based chemotherapy in the treatment of MCRC.
Materials and methods We performed a computerized search using combinations of the following keywords: “metastatic colorectal cancer,” “Xeloda,” “chemotherapy,” “capecitabine,” or “5-fluorouracil.”
Results Treatment with capecitabine chemotherapy was associated with a significantly prolonged progression-free survival (WMD = 1.24; 95% CI, 0.04–2.44; P = 0.04), whereas overall survival was not statistically significant (WMD [random] = 0.29; P = 0.75). Patients in both capecitabine and 5-fluorouracil groups had equal 1-, 2-, and 3-year survival (OR = 0.82, 95% CI: 0.59–1.12, P = 0.21; OR = 0.84, 95% CI: 0.61–1.15, P = 0.27; OR = 1.26, 95% CI: 0.78–2.05, P = 0.34, respectively). The analysis also demonstrates that the response rate of capecitabine-based chemotherapy was comparable to 5-fluorouracil-based chemotherapy (OR = 1.02, 95% CI, 0.90–1.14; P = 0.80). When comparing single-agent capecitabine against 5-fluorouracil/leucovorin, our results showed an overall OR of 1.56 (95% CI, 1.16–2.09) in favor of the capecitabine arm. When toxicity was evaluated, a statistically significant benefit with capecitabine-based therapy was seen, especially for grade 3/4 neutropenia (OR, 0.80; 95% CI, 0.71–0.91; P = 0.00005).
Conclusions Capecitabine-based chemotherapy demonstrated a significantly superior progression-free survival, equivalent overall survival, and comparable response rate with 5-fluorouracil-based chemotherapy. These observations support the use of capecitabine-based chemotherapy in the treatment of MCRC as a first-line or as a neoadjuvant modality.

Keywords Capecitabine · 5-fluorouracil · Metastatic colorectal cancer · Meta-analysis

Introduction

Despite advances in early diagnosis and treatment, colorectal cancer (CRC) remains a significant public health concern and is the third leading cancer in both men and women. Upon diagnosis, 19% of colorectal cancer cases are metastatic. The overall 5-year survival rate for patients with colorectal cancer is 63%, whereas the rate drops to 10% or even less in patients with metastatic disease (Jemal et al. 2005). For more than four decades, 5-fluorouracil (5-FU) in combination with folic acid (leucovorin, LV) had been the mainstay of palliative therapy for metastatic colorectal cancer (MCRC), with median survival at approximately 12 months. Current standard first-line regimens for MCRC are FOLFOX (infusional 5-FU/LV with oxaliplatin) and FOLFIRI (infusional 5-FU/LV with irinotecan). A drawback of the infusional 5-FU regimen is the
Capecitabine as Adjuvant Treatment for Stage III Colon Cancer

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ABSTRACT

BACKGROUND

Intravenous fluorouracil plus leucovorin is the standard adjuvant treatment for colon cancer. The oral fluoropyrimidine capecitabine is an established alternative to bolus fluorouracil plus leucovorin as first-line treatment for metastatic colorectal cancer. We evaluated capecitabine in the adjuvant setting.

METHODS

We randomly assigned a total of 1987 patients with resected stage III colon cancer to receive either oral capecitabine (1004 patients) or bolus fluorouracil plus leucovorin (Mayo Clinic regimen; 983 patients) over a period of 24 weeks. The primary efficacy end point was at least equivalence in disease-free survival; the primary safety end point was the incidence of grade 3 or 4 toxic effects due to fluoropyrimidines.

RESULTS

Disease-free survival in the capecitabine group was at least equivalent to that in the fluorouracil-plus-leucovorin group (in the intention-to-treat analysis, P<0.001 for the comparison of the upper limit of the hazard ratio with the noninferiority margin of 1.20). Capecitabine improved relapse-free survival (hazard ratio, 0.86; 95 percent confidence interval, 0.74 to 0.99; P=0.04) and was associated with significantly fewer adverse events than fluorouracil plus leucovorin (P<0.001).

CONCLUSIONS

Oral capecitabine is an effective alternative to intravenous fluorouracil plus leucovorin in the adjuvant treatment of colon cancer.

*Other investigators in the Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial are listed in the Appendix.
CAPECITABINE AS ADJUVANT TREATMENT FOR COLON CANCER


REFERENCES

DESCRIPTION: XELODA (capecitabine) is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5′-deoxy-5-fluorouridine (5′-DFUR) which is converted to 5-fluorouracil.

The chemical name for capecitabine is 5′-deoxy-5-fluoro-N-[pentyloxy]carbonyl]-cytidine and has a molecular weight of 359.35. Capecitabine has the following structural formula:

![Capecitabine Structure]

Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20°C.

XELODA is supplied as biconvex, oblong film-coated tablets for oral administration. Each light peach-colored tablet contains 150 mg capecitabine and each peach-colored tablet contains 500 mg capecitabine. The inactive ingredients in XELODA include: anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate and purified water. The peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

CLINICAL PHARMACOLOGY: Capecitabine is relatively non-cytotoxic in vitro. This drug is enzymatically converted to 5-fluorouracil (5-FU) in vivo.

Bioactivation: Capecitabine is readily absorbed from the gastrointestinal tract. In the liver, a 60 kDa carboxyesterase hydrolyzes much of the compound to 5′-deoxy-5-fluorocytidine (5′-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5′-DFCR to 5′-deoxy-5-fluorouridine (5′-DFUR). The enzyme, thymidine phosphorylase (dTThdPase), then hydrolyzes 5′-DFUR to the active drug 5-FU. Many tissues throughout the body express thymidine phosphorylase. Some human carcinomas express this enzyme in higher concentrations than surrounding normal tissues.
XELODA® (capecitabine)

become serious. Your doctor may instruct you to decrease the dose and/or temporarily discontinue treatment with XELODA.

STOP taking XELODA immediately and contact your doctor if any of these symptoms occur:

- **Diarrhea**: if you have more than 4 bowel movements each day or any diarrhea at night.
- **Vomiting**: if you vomit more than once in a 24-hour time period.
- **Nausea**: if you lose your appetite, and the amount of food you eat each day is much less than usual.
- **Stomatitis**: if you have pain, redness, swelling, or sores in your mouth.
- **Hand-and-foot syndrome**: if you have pain, swelling or redness of hands and/or feet.
- **Fever or Infection**: if you have a temperature of 100.5°F or greater, or other evidence of infection.

If caught early, most of these side effects usually improve within 2 to 3 days after you stop taking XELODA. If they don’t improve within 2 to 3 days, call your doctor again. After side effects have improved, your doctor will tell you whether to start taking XELODA again or what dose to use.

**How should I store and use XELODA?**

- Never share XELODA with anyone.
- XELODA should be stored at normal room temperature (about 65° to 85°F).
- Keep this and all other medications out of the reach of children.
- In case of accidental ingestion or if you suspect that more than the prescribed dose of this medication has been taken, contact your doctor or local poison control center or emergency room IMMEDIATELY.
- Medicines are sometimes prescribed for uses other than those listed in this leaflet. If you have any questions or concerns, or want more information about XELODA, contact your doctor or pharmacist.

* Taxol is a registered trademark of Bristol-Myers Squibb Company.
† Adriamycin is a registered trademark of Pharmacia & Upjohn Company.
‡ Dilantin is a registered trademark of Parke-Davis.
§ Coumadin is a registered trademark of DuPont Pharma.
Capecitabine: An In-vitro Comparison between the Branded Xeloda® 500 Mg and its Intended Copy Capeda 500 Mg

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Abstract
Introduction: Dissolution is an example of in-vitro test which can be used to identity formulations that may present potential bioequivalence problems. It is defined as the amount of substance that goes into solution per unit time under standardised conditions of liquid/solid interface, solvent composition and temperature. It is considered one of the most important tools to predict the in-vivo bioavailability and in some cases replacing clinical studies to determine bioequivalence.

Aim: To compare the differences in the dissolution behaviour between two anticancer formulations, Xeloda® 500 mg (reference product) and Capeda 500 mg (test product).

Methods: Four replicates for each batch of the tested medicines were carried out using a PT-DT70 dissolution tester (Pharma Test) to detect any differences in their dissolution behaviour. Samples at nine time intervals were tested according to the US Pharmacopeia with the rate of dissolution determined by ultra-violet spectrophotometry.

Results: All the tested medicines complied with the pharmacopoeial specifications, the EMA and the FDA guidance for industry when achieved 85% dissolution in 60 minutes. However, Capeda 500 mg (test product) showed slower, different and incomplete dissolution rate compared to Xeloda® 500 mg (reference product) at both 60 and 120 minutes. Other visual differences in the weight, size, clarity of solution, presence of undissolved residue and particles during the dissolution test were also detected.

Conclusion: Results in this study clearly raise a question about the interchangeability between Xeloda® 500 mg and its intended copy Capeda 500 mg. Awareness of these scientific concerns should be considered when a clinical choice between these two drugs is required. Differences between the innovator and copy medicines with regard to pharmacokinetics, clinical efficacy and safety may exist. Thereby, patients’ monitoring after performing drug substitution of these two medicines is strongly recommended.

Keywords: Dissolution test; Differences between the branded and generic medicines; Absorption and dissolution methods; Capecitabine; Xeloda®; Capeda

Introduction

Generic drug usually means a drug that has the same qualitative and quantitative composition of the active ingredient and the same pharmaceutical form as the reference branded drug, and whose bioavailability with the reference drug has been demonstrated by an appropriate bioequivalence study [1]. Generic substitution is defined as switching between a branded product and a generic version of the same drug (such as switching from Taxotere® to docetaxel) [2]. Promoting generic substitution from multiple sources into the healthcare system is aimed at maximising population health subject to improve the overall healthcare delivery systems [3]. This strategy of drug substitution is proven to be effective since it is often easier to intervene on the expenditure of medicines because of their identical cost [4-6]. However, this has been accompanied by a variety of problems of which the most critical is the widespread distribution of substandard generics and fake drug products. As a consequence, health care providers and patients are usually concerned when selecting one drug from among several bioequivalent ones during the treatment regimen [7, 8].

Dissolution is an example of in-vitro test which can be used to identify formulations that may present potential bioequivalence problems. It is defined as the amount of substance that goes into solution per unit time under standardised conditions of liquid/solid interface, solvent composition and temperature [9]. It is considered one of the most important tools to predict the in-vivo bioavailability and in some cases replacing clinical studies to determine bioequivalence [10]. Dissolution is considered as the rate limiting step for a drug to be absorbed from solid dosage form following oral administration. It is the process of transporting the drug substances from the gastrointestinal lumen into the systemic circulation [11]. Absorption is the first step before the distribution, metabolism and elimination (ADME) of drugs in the human body. It usually depends on the stages of disintegration, disaggregation, drug release from the pharmaceutical form, its dissolution under physiological conditions and permeability through the biological membranes, (Figure 1) [12, 13].

In the cases when the in-vitro results fail to predict the in-vivo performance of a drug product, larger clinical studies are needed to assess the product bioavailability, thus additional cost will be added to the drug development expenses [14]. Therefore, dissolution is considered one of the most important quality control tests performed on pharmaceutical dosage forms and validation of dissolution methods and is an important part of good manufacturing practice [9]. The importance of dissolution testing, for example, has recently directed the UK MHRA (Medicines and Healthcare products Regulatory Agency) to suspend the license of the generic Tera (levohydroxine 100

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Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer

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ABSTRACT

BACKGROUND
The management of metastatic breast cancer requires monitoring of the tumor burden to determine the response to treatment, and improved biomarkers are needed. Biomarkers such as cancer antigen 15-3 (CA 15-3) and circulating tumor cells have been widely studied. However, circulating cell-free DNA carrying tumor-specific alterations (circulating tumor DNA) has not been extensively investigated or compared with other circulating biomarkers in breast cancer.

METHODS
We compared the radiographic imaging of tumors with the assay of circulating tumor DNA, CA 15-3, and circulating tumor cells in 30 women with metastatic breast cancer who were receiving systemic therapy. We used targeted or whole-genome sequencing to identify somatic genomic alterations and designed personalized assays to quantify circulating tumor DNA in serially collected plasma specimens. CA 15-3 levels and numbers of circulating tumor cells were measured at identical time points.

RESULTS
Circulating tumor DNA was successfully detected in 29 of the 30 women (97%) in whom somatic genomic alterations were identified; CA 15-3 and circulating tumor cells were detected in 21 of 27 women (78%) and 26 of 30 women (87%), respectively. Circulating tumor DNA levels showed a greater dynamic range, and greater correlation with changes in tumor burden, than did CA 15-3 or circulating tumor cells. Among the measures tested, circulating tumor DNA provided the earliest measure of treatment response in 10 of 19 women (53%).

CONCLUSIONS
This proof-of-concept analysis showed that circulating tumor DNA is an informative, inherently specific, and highly sensitive biomarker of metastatic breast cancer. (Funded by Cancer Research UK and others.)
Screening for colorectal cancer

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Screening for colorectal cancer is feasible and there is increasingly compelling evidence to show that such programmes can save lives at a cost similar to that of the existing breast cancer screening programme.

Colorectal cancer is the third commonest malignancy in the UK, killing around 20,000 people per annum. Colorectal cancer is equally prevalent in men and women, and usually occurs in later life (aged 60–70 years). The incidence and mortality of colorectal cancer have remained approximately static for the past 40 years, although there are recent trends showing slight declines in both in the UK and in the US. The decrease in mortality may reflect a tendency towards earlier diagnosis, possibly as a result of increased public awareness of the disease. Surgery remains the mainstay of treatment for colorectal cancer, but early diagnosis makes it more likely that the tumour can be completely resected and thereby improves the chance of a cure.

Early diagnosis in colorectal cancer is challenging because the symptoms of bowel cancer are very similar to the symptoms of a number of benign bowel conditions such as haemorrhoids, irritable bowel syndrome and diverticular disease. Population screening may provide a good opportunity to improve survival and reduce the incidence of this important condition, but which test and can we afford it?

Why screen for colorectal cancer?

It is widely accepted that the vast majority of colorectal cancers result from malignant change in polyps (adenomas) occurring in the lining of the bowel 10–15 years before malignant change occurs. The best available evidence suggests that only 10% of 1 cm adenomas undergo malignant change after 10 years. The incidence of adenomatous polyps in the colon increases with age, and although adenomatous polyps can be identified in up to 20% of the population, most of these are small and unlikely to undergo malignant change. The vast majority (90%) of adenomas can be removed at colonoscopy, obviating the need for surgery. Other types of polyps occurring in the colon such as metaplastic
cancer leads to false re-assurance from negative tests. However, there are complications from colonoscopy (perforation and haemorrhage). The incidence of these complications is around 1 in 2000 procedures, and usually occurs in therapeutic colonoscopy (endoscopic polypectomy) rather than in diagnostic procedures. Mortality from such events is fortunately very rare.

**Key points for clinical practice**

- Screening for colorectal cancer using faecal occult blood tests is feasible and there is increasingly compelling evidence to show that such programmes can save lives at a cost similar to that of the existing breast cancer screening programme.
- Only flexible sigmoidoscopy presents a promising alternative to faecal occult blood screening, but conclusive data will not be available for another 5–7 years.
- To undertake such a programme in the UK, there would need to be a considerable investment in colonoscopy facilities and expertise.
- Several countries, including the US, have instituted screening programmes utilising one or both of these modalities. Whether the UK follows will be determined by political decisions.

**Bibliography**


