SINGLE- AGENT CAPECITABINE AS FIRST- LINE TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER

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RESUME:

Background: Capecitabine is an oral fluoropyrimidine carbamate that is at least as effective than Fluorouracil / Leucovorin as first- line treatment for patients with metastatic colorectal cancer /CRC/. **Aim:** The aim of this study was to evaluate the efficacy and toxicity of single- agent Capecitabine as first- line therapy in patients with metastatic CRC. **Methods:** In the period 2007- 2009 17 consecutive patients with /CRC/ entered the study. The treatment schedule consists of Capecitabine 1250 mg/m^2 p.o. twice daily for 14 days with a 7- day rest period. **Results:** Overall response rate was 23,6% with one complete remission. Median survival was 12,4 months. Nausea, vomiting and diarrhea were the most common side effects. **Conclusions:** That data suggest that single- agent Capecitabine will offer opportunity to treat patients with advanced /CRC/.

Key words: Metastatic colorectal cancer, First- line therapy, Single- agent Capecitabine, Survival

INTRODUCTION

Colorectal cancer /CRC/ is the third most commonly diagnosed malignancy, accounting for 10% to 15% of newly diagnosed cancer cases in Europe and United States. An estimated 783 000 new cases are diagnosed annually worldwide /1/. Up to 30% of patients present with metastatic disease, and approximately 50% to 60% eventually develop metastases or advanced disease. The prognosis for these patients is bleak, with 5- year survival rates of 5% or less /2/.

The most widely used agent in the treatment of metastatic CRC is 5- Fluorouracil /FU/, which was developed more than 50 years ago and is included in most regime of palliative chemotherapy for CRC /3/. A fluorinated pyrymidine, FU acts by inhibiting thymidylate synthase, an enzyme necessary for the production of thymidine nucleotides required for DNA synthesis. Numerous attempts have been made to improve the efficacy of FU, including biomodulation and schedule modification. Protracted infusion of FU and biomodulation with agents such as Leucovorin /LV/ have both resulted in improved response rates compared with bolus FU alone, but neither approach has demonstrated a clinically meaningful benefit in randomized trials or meta- analyses /4/.

An alternative approach to optimizing FU- based therapy has been the development of oral fluoropyrimidine derivates designed to deliver FU to the target cells. Oral administration enables sustained exposure to FU, avoids the technical barriers of intravenous administration and allows significant flexibility in the choice of the dosage regimen. In addition, most patients prefer oral cytotoxic therapy to intravenous regimens, provided that efficacy is not compromised /5/.

Capecitabine, an oral fluoropyrimidine carbamate, was rationally designed to generate FU predominantly within tumor cells /6/. After rapid and extensive absorption as an intact molecule, capecitabine is converted to 5-FU predominantly in tumor tissue by exploiting the high activity of thymidine phosphorylase in malignant tissue /7/. The enzymatic conversion of capecitabine occurs in three steps. In the first stage, capecitabine is hydrolyzed by hepatic carboxylesterase to 5'-deoxy-5-fluorocytidine. This intermediate is then converted to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine- deaminase in tumor cells and the liver. The third and final step involves the conversion of 5'-DFUR to FU by thymidine phosphorylase and occurs predominantly in tumor tissue as result of the high activity of thymidine phosphorylase /8/. The increasing specificity for tumor cells occurring with each successive conversion step potentially reduces systemic 5-FU exposure while increasing the 5-FU dose within tumor tissue. The tumor selectivity of Capecitabine has been confirmed in patients with colorectal cancer. Patients received Capecitabine 1250 mg/m2 twice daily for 5 to 7 days before surgical resection of their primary tumor and/or liver metastases. Concentrations of FU in primary tumor tissue were 3,2- fold higher than in adjacent healthy tissue and 21-f old higher than in plasma /9/.

Capecitabine was compared with bolus FU/LV as first-line chemotherapy in two large randomized trials in metastatic CRC. Although no differences in terms of median time to disease progression and overall survival were found in both trial, one study showed a significantly higher response rate for Capecitabine- 26% compared with 12%, p< 0,0001 /10/.

The aim of this study was to evaluate the efficacy and safety of single- agent Capecitabine as first- line chemotherapy in patients with metastatic CRC.

PATIENTS AND METHODS

Seventeen consecutive patients with metastatic CRC, treated in the period 2007- 2009 in Medical University- Pleven, Oncological center, Department of chemotherapy, entered the study. Participants needed to be between 18 and 75 years of age. Eligibility criteria included histologically documented adenocarcinoma of the colon or rectum, progressive measurable metastatic disease, life expectancy of minimum three months, World Health Organisation /WHO/ performance status 0 to 2, no prior chemotherapy for metastatic disease, adequate bone marrow function /absolute granulocyte count > $1,5x10^9$/L, platelet count > $140x10^9$/L/ as well as normal renal /serum creatinine level < 1,5 μmol/L/ and hepatic function / serum bilirubin level < 21 μmol/L/, absence of active infections, no overt cardiac disease and at least one measurable tumour lesion. Measurable disease was assessed by computed tomography scan. This study required that previous adjuvant FU- based therapy be completed at least 6 months prior start of treatment. Patients with central nervous system metastases, bowel obstruction or ileus were excluded from the study. Capecitabine was administered orally at a dose of 1250 mg/m2 twice daily as an intermittent regimen in 3- week cycles- 2 weeks of treatment followed by 1 week of rest. Capecitabine was given at approximately 12 hours intervals orally with water within 30 min of ingesting food. Treatment was continued until disease progression, unacceptable adverse effects or the withdrawal of patient consent. Patients were evaluated for tumour response before treatment and after third and sixth course of chemotherapy. Tumour response was evaluated according to WHO response criteria /11/. Response was defined as complete response (CR), partial response (PR), no change (NC), or progressive disease (PD). A CR was defined by the disappearance of all known disease, confirmed by two observations not less than 4 weeks apart. PR was defined as a decrease in tumour size of 50% or more (either measured or estimated in the case of measurable or assessable disease). In addition, there could be no appearance of any new lesions or progression of any known lesion(s). Objective tumour response included both confirmed CR and PR. Safety was assessed using the WHO toxicity criteria /12/.

The duration of response was calculated from the day of the start of treatment to disease progression; overall survival was measured from study entry to death. The time to disease progression was calculated from study entry until the day of the first evidence of disease progression. The actuarial survival was estimated by the method of Kaplan and Meyer /13/.

RESULTS

Patients and Treatment

A total of 17 patients were entered in the study over an 18- months period. All patients, regardless of their length of treatment, were included in analysis. Antitumour effects were evaluated for all 17 cases. Table 1 lists demographic data, baseline disease characteristics and prior therapy for all patients. As expected, most patients were elderly, and the rectum was the most common site of primary tumour. All patients had advanced or metastatic disease, and the most frequently metastatic site were liver, lung and peritoneum. Median treatment period was 6,5 months. The most frequent reason for treatment discontinuation was progressive disease. The safety was assessed in all 17 patients. The median follow-up period was 11,5 months.

Antitumour effects

The resulting antitumour effects are presented in Table 2. One complete and three partial remissions were obtained. The overall response rate /ORR/ was 23,6 % (4 of 17), showing that chemotherapy had induced a moderate efficacy. Median time to disease progression was 3,8 months. A one-year survival rate was 73, 5%. Regression analysis identified elevated alkaline phosphatase at baseline, poor WHO performance status, multiple site of metastases and liver as predominant site of metastases as prognostic factors, correlated with reduced overall survival.

Safety

Table 3 and 4 presents the incidence of haematological and nonhaematological adverse drug reactions that occurred in entire group. The highest incidence was gastrointestinal, haematology and mucositis. Most of these symptoms were rated as grade II or I and chemotherapy was not stopped or delays. Grade III- IV gastrointestinal and haematology toxicity was observed in 14,2 % of the patients and never was fatal.

DISCUSSION

In the current study we evaluated efficacy and safety of the Capecitabine as first- line chemotherapy for metastatic colorectal cancer. Response rate- 23,6% is promising. These results are comparable with previously published data. In these studies response rate were 20- 43% with time to progression of 3-6 months. Tumour control /CR= PR+ SD/ was achieved in more than 70% of patients with survival duration 12,4 months and is similar to other reports /10,14/

In the majority of patients the chemotherapy regimen was well tolerated. Both haematological and nonhaematological toxicity was mild to moderate and chemotherapy was not stopped because of toxicity. Gastrointestinal toxicity or mucositis never was fatal. Delayed diarrhea, a well-known side effect of Capecitabine was generally managed with loperamide, which was administered to approximately one third of patients.

In conclusion, the results of the present study indicate that the treatment with capecitabine for patients with metaststic CRC appears promising with of survival rate of 12,4 months and moderate toxicity.

Table 1. Patient characteristics

Patient characteristics	Number of patients
Age (years)	41 – 75
Sex	
Males	13
Females	4
Primary tumour site	
Colon	6 (35,2%)
Rectum	11 (64,8%)
Dominant site of metastasis	
Liver	9 (52,9%)
Lung	6 (35,4%)
Peritoneum	2 (11,7%)
N of metastatic sites	
1	12 (70,5%)
2	3 (17,8%)
3	2 (11,7%)
Previous treatment	
Surgery	5 (29,4%)
Surgery+ radiotherapy	7 (41,2%)
Surgery+ chemotherapy	5 (29,4%)
Performance status	
0	6 (35,4%)
1	9 (52,9%)
2	2 (11,7%)

Table 2. Objective responses

Patients/ Response	CR	PR	NC	PD	ORR%
17	1	3	8	5	23,6%

ORR= CR + PR .

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; ORR, overall objective response rates;

Table 3. Adverse drug reactions by symptoms: grade 3 and 4 non-hematological toxicities

Adverse drug reactions	Number of patients
Acute diarrhea	3 (17,6 %)
Delayed diarrhea	2 (11,7 %)
Nausea	3 (17,6 %)
Mucositis	2 (11,7 %)
Fever	1 (5,9 %)
Obstipatio	1 (5,9 %)
Alopecia	1 (5,9 %)

Table 4. Adverse drug reactions by symptoms: grade 3 and 4 haematological toxicities

Adverse drug reactions	Number of patients
Leucopenia	2 (11,7 %)
Thrombocytopenia	1 (5,9 %)
Anaemia	1 (5,9 %)

REFERENCES

1. Jemal A, Tiwari RC, Murray T. et al, Cancer Statistics, 2004. CA Cancer J Clin, 2004; 54:8–29

2. Wingo PA, Ries LA, Parker SL, et al, Long- terms cancer patient survival in the United States. Cancer Epidemiol Biomarkers Prev, 1998; 7:271-282

3. Benson AB III: Therapy for advanced colorectal cancer. Semin Oncol, 1998 (suppl 11); 25:2-11

4. Advanced Colorectal Cancer Meta-Analysis Project: Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: Evidence in terms of response rate. J Clin Oncol , 1992; 10:896-903

5. Meropol NJ: Oral fluoro-pyrimidines in the treatment of colorectal cancer. Eur J Cancer, 1998; 34:1509-1513

6. Ishikawa T, Utoh M, Sawada N, et al: Tumor selective delivery of 5-fluorouracil by capecitabine, a new oral fluoropyrimidine carbamate, in human cancer xenografts. Biochem Pharmacol, 1998; 55:1091-1097

7. Miwa M, Ura M, Nishida M, et al: Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer, 1998; 34:1274-1281

8. Mackean M, Planting A, Twelves C, et al: Phase I and pharmacologic study of intermittent twice-daily oral therapy with capecitabine in patients with advanced and/or metastatic cancer. J Clin Oncol, 1998; 16:2977-2985

9. Schuller J, Cassidy J, Dumont E, et al: Preferential activation of capecitabine in tumor following oral administration in colorectal cancer patients. Cancer Chemother Pharmacol, 2000; 45:291-297

10. Hoff PM, Ansari R, Batist G et al, Comparison of oral capecitabine versus intravenous 5- fluorouracil plus leucovorin /Mayo Clinic regimen/ as first- line treatment in 605 patients with metastatic colorectal cancer. Results of

a randomized phase III study. J Clin Oncol, 2001; 19: 2282- 2292

11. Miller AB, Hoogstraten B, Staquet M et al. Reporting results of cancer treatment. Cancer 1981; 47; 207-214

12. Brimdage MD, Pater JL, Zee B: Assessing the reliability of two toxicity scales: Implications for interpreting toxicity data. J Natl Cancer Inst 1993; 85; 38-48

13. Kaplan EL, Meyer P: Non-parametric estimation from incomplete observations. J Am Stat Assoc 1959; 53; 457- 481

14. Van Gustem E., Twelwes C, Cassidi J. et al, Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol, 2001; 19: 4097- 4106

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OUR EXPERIENCE WITH IRINOTECAN AND BOLUS FLUOROURACIL / LEUCOVORIN IN THE TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER

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RESUME:

Background: Irinotecan is a topoisomerase I inhibitor that prolongs survival as first- line therapy in patients with advanced or metastatic colorectal cancer **Aim:** The aim of this study was to evaluate the efficacy and toxicity of Irinotecan combined with bolus Fluorouracil and Leucovorin. **Methods:** In the period 2006- 2008 38 consecutive patients with metastatic colorectal cancer entered the study. The treatment schedule consists of Irinotecan 180 mg/m^2 i.v. day 1, Fluorouracil i.v. bolus 450 mg/m^2 days 2- 5 and Leucovorin i.v. bolus 35 mg/m^2 day 2- 5 with repetition every 21 days. **Results:** Overall response rate was 34,2% with two complete remissions. Median survival was 15,4 months. Diarrhea, nausea, vomiting and mucositis were most common side effects. **Conclusions:** The combination of Irinotecan with bolus Fluorouracil / Leucovorin as first- line therapy for patients with metastatic colorectal cancer offer consistently improved tumour control and prolonged survival.

Key words: Metastatic colorectal cancer, First- line reatment, Irinotecan, Response rate

INTRODUCTION

Colorectal cancer /CRC/ is the third in the league cancer death worldwide with more than 204 000 deaths in Europe each year /1/. Approximately 25% of CRC patients presents with overt metastases, and an additional 25- 35% of patients will develop metastases during the course of their disease /2/. Significantly between 20% and 30% of patients with advanced CRC have liver only metastases, while approximately 50% of recurrences following resection of primary tumour are localized to the liver /3/. Liver resection offers the only chance of cure for such patients, with five-year survival rates following resection range between 25% and 40% compared with between 0% and 5% for patients who did not undergo liver resection /4/. However, approximately 85% of patients with stage IV CRC have metastatic liver disease which is considered to be unresectable at presentation /5/. Palliative chemotherapy is more effective than the best supportive care in improving survival as well as the quality of life in such patients /6/. 5-Fluorouracil /FU/ is the most commonly used agent for treatment of metastatic CRC for over 50 years /7/. A