

## A Phase II Study of Capecitabine Combined with Gemcitabine in Patients with Advanced Gallbladder Carcinoma

Jae-Yong Cho,<sup>1</sup> Ji-Sun Nam,<sup>1</sup> Mi-Suk Park,<sup>2</sup> Jeong-Sik Yu,<sup>2</sup> Yong-Han Paik,<sup>1</sup> Se-Joon Lee,<sup>1</sup> Dong-Ki Lee,<sup>1</sup> and Dong-Sup Yoon<sup>3</sup>

Departments of <sup>1</sup>Internal Medicine, <sup>2</sup>Diagnostic Radiology, <sup>3</sup>Surgery, Yongdong Severance Hospital Pancreatobiliary Clinic, Yonsei University College of Medicine, Seoul, Korea.

Capecitabine and gemcitabine are used in the treatment of a variety of solid tumors including pancreatic and biliary tract carcinomas. The authors evaluated survival, response, and toxicity associated with using a combination of capecitabine and gemcitabine to treat patients with unresectable or metastatic gallbladder adenocarcinoma (GBC). Eligible patients had histologically- or cytologically-confirmed GBC, no prior systemic therapy with capecitabine or gemcitabine, Karnofsky Performance Status 70%, serum total bilirubin up to three times normal, and measurable disease. Treatment consisted of gemcitabine 1000 mg/m<sup>2</sup> IV on Days 1 and 8 concurrent with administration of capecitabine 1000 mg/m<sup>2</sup> PO BID on Days 1 through 14, on a 3-week cycle. Tumor response was assessed by the response evaluation criteria in solid tumors (RECIST criteria) and survival was calculated from initiation of CapGem therapy. A total of 24 patients were enrolled. Median age at the time of diagnosis was 62 years (range, 41-78 years). Fourteen patients had undergone prior surgery. Results showed that eight patients achieved partial response (33%) with an additional 10 patients achieving stable disease (42%). The overall median time to disease progression was 6.0 months (95% CI, 3.8-8.1 months) and overall survival was 16 months (95% CI, 13.8-18.3 months). The one-year survival rate was 58%. No Grade 4 toxicity was seen. Transient Grade 3 neutropenia/thrombocytopenia and manageable nausea, hand-foot syndrome and anorexia were the most common toxicities. Our study shows that CapGem is an active and well-tolerated chemotherapy regimen in patients with advanced GBC.

**Key Words:** Capecitabine, gemcitabine, gallbladder cancer

Received March 24, 2005

Accepted May 13, 2005

Reprint address: requests to Dr. Jae Yong Cho, Department of Internal Medicine, Yongdong Severance Hospital, Yonsei University College of Medicine, 146-92 Dogok-dong, Kangnam-gu, Seoul 135-720, Korea. Tel: 82-2-3497-3310, Fax: 82-2-3463-3882, E-mail: chojy@yumc.yonsei.ac.kr

## INTRODUCTION

Most patients with GBC present with invasive, inoperable disease. Chemotherapeutic agents including 5-fluorouracil (5-FU), mitomycin C, cisplatin, methotrexate, etoposide, and doxorubicin have been tried alone, and in combination, for this patient group. Partial responses lasting from weeks to several months have been observed only in about 10-20% of the cases, and the median survival for patients with gallbladder cancer is dismal at around four months.<sup>1</sup> Chemo-immunotherapy has shown encouraging results,<sup>2,3</sup> but the data are limited to a few case reports only. Similarly, isolated reports of intra-arterial chemotherapy<sup>4</sup> and intra-lesional therapy<sup>5</sup> have been published. The poor therapeutic results, along with small sample sizes in the trials, preclude the support of any particular chemotherapeutic regimen for unresectable disease. Therefore, newer, more effective treatment strategies must be evaluated.

Several reports have suggested that gemcitabine (Gemzar<sup>®</sup>; Eli Lilly, Indianapolis, IN, USA) may act on biliary tract tumors and GBC.<sup>6,7</sup> A subsequent Phase II studies using a weekly dose of 1000 mg/m<sup>2</sup> of gemcitabine for three out of four weeks showed a 36% partial response rate in a group of 26 patients with metastatic or unresectable GBC.<sup>8</sup> In a Phase II trial of 1,200 mg/m<sup>2</sup> of gemcitabine given weekly for three weeks followed by a two-week rest period, 3 of 19 patients with biliary tract cancer or GBC (16%) achieved a

partial response.<sup>9</sup> The median survival period was 6.5 months and the time to disease progression was 2.5 months. A Phase II trial of gemcitabine given every other week at a dose of 2,200 mg/m<sup>2</sup> reported a response rate of 22% and a median survival period of 11.5 months.<sup>10</sup> The combination of gemcitabine, 5-FU, and leucovorin (LV) has been evaluated in several Phase I trials, building on preclinical studies demonstrating synergistic and additive effects in an *ex vivo* tumor model.<sup>11</sup> Three Phase I studies evaluating the combination of gemcitabine, 5-FU, and LV have been completed to date.<sup>12,13</sup> All these studies showed evidence of meaningful antitumor activity and few significant side effects. Capecitabine (Xeloda<sup>®</sup>; Hoffman La Roche, Basel, Switzerland) is a selective, oral fluoropyrimidine carbamate that generates 5-FU selectively in tumor tissues. This selectivity is achieved by the enzyme thymidine phosphorylase, which is responsible for the final conversion of capecitabine to 5-FU and is found at much higher levels in cancers compared with normal tissues.<sup>14-16</sup> Capecitabine offers the possibility of continuous tumor exposure to 5-FU by preferential activation at the tumor site, while potentially minimizing the exposure of healthy body tissues to systemic 5-FU.<sup>17,18</sup> We performed this study to further investigate the potential of CapGem in previously untreated patients with advanced and/or metastatic GBC.

## MATERIALS AND METHODS

### Eligibility

Patients with histologically confirmed unresectable or metastatic GBC, who were at least 18 years of age and who had a Karnofsky Performance Status of >70% were included. The following hematologic and chemistry parameters were recommended: neutrophils > 1.5 × 10<sup>9</sup>/L, platelet count > 100 × 10<sup>9</sup>/L, total bilirubin level < three times the upper limit of normal, aspartate aminotransferase (AST) level < five times the upper limit of normal, and creatinine level < one and a half times the upper limit of normal. Previous use of capecitabine or gemcitabine, and previous receipt of radiation therapy to more than

25% of the bone marrow were the exclusion criteria. Pregnant or lactating patients were excluded from the study. Female participants were required to use adequate contraceptive methods to prevent pregnancy during treatment. Other contraindications included a history of brain or other central nervous system metastases. Previous biologic or immunologic therapy was not allowed within four weeks of study entry. Any history of a previous malignancy diagnosed within five years was not allowed, with the exception of basal or squamous cell carcinoma or skin and cervical carcinoma *in situ*.

### Treatment and dose modification

Capecitabine (1,000 mg/m<sup>2</sup>) was administered orally twice a day for 14 consecutive days followed by one week of rest. Gemcitabine was given as a 30 min IV infusion on Days 1 and 8 of each cycle at a dose of 1,000 mg/m<sup>2</sup>. Cycles were repeated every 21 days provided that patients had recovered sufficiently from the drug-related side effects. Prophylactic administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF) was not allowed. In cases where the patient had Grade 3 or 4 afebrile neutropenia, subsequent cycles were repeated with rhG-CSF prophylactic administration. If the patient had febrile neutropenia or Grade 3 or 4 neutropenia despite the prophylactic administration of rhG-CSF, capecitabine and gemcitabine doses were reduced by 25%. In cases of Grade 3 or 4 thrombocytopenia lasting for more than 5 days, the doses of both drugs were also reduced by 25%. The dose of capecitabine was reduced by 25% in cases of Grade 3 or 4 diarrhea or hand-foot syndrome.

### Efficacy and safety evaluation

Tumor assessments according to RECIST criteria were performed at six-week intervals by the investigators. Tumor lesions were assessed by computed tomography (CT) scanning, X-rays or magnetic resonance imaging (MRI); objective tumor response was based on the dimensions of measurable marker lesions, measured by the same radiologist throughout the study. Time to progres-

sion (TTP) was calculated as the time from the first treatment to the time the patient was first recorded as having progressive disease (PD), or the date of death if the patient died before PD was demonstrated. Survival was monitored every three months after the patient completed treatment. Safety was monitored throughout the study and for 28 days after the last study treatment. Adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC). Hand-foot syndrome was graded as in previous capecitabine studies.<sup>19</sup> TTP and survival were analyzed by the Kaplan-Meier product limit method. Those who did not receive at least one dose of study medication or for whom no follow-up safety information was available were excluded from the safety analysis.

## RESULTS

### Patient characteristics

Twenty-four patients (18 women and 6 men) were enrolled between June 2001 and December 2004. Patients who received at least one dose of CapGem were considered evaluable for efficacy and safety. As shown in Table 1, the majority of patients (75%) had Stage IV disease and the most commonly affected metastatic sites were the liver (67%) and the lymph nodes (54%). Fourteen patients had undergone one or more type of surgery.

### Treatment administration

A median of four courses of treatment (range, 1-16 courses) were given. Reasons for discontinuing study treatment included disease progression (79%), toxicity (10%), or other reasons (11%). During Cycle 1, 96.7% (range, 86-100%) and 98.7% (range, 87-100%) of the planned dose of capecitabine and gemcitabine, respectively, were given. During Cycle 2, 95.1% (range, 83-100%) and 96.3% (range, 85-100%) of the planned doses of capecitabine and gemcitabine, respectively, were given. Despite the need for dose modifications, 90% of patients received all three weeks of treatment with both drugs during the first two cycles of therapy.

**Table 1.** Patient Characteristics

Variables	No. (%)
Total No. of patients treated	24
Age (yrs)	
Median	62
Range	41 - 78
Sex	
Male	6 (25)
Female	18 (75)
Karnofsky performance status (%)	
Median	90
Range	70 - 100
Disease stage	
Locally advanced	12 (50)
Metastatic	18 (75)
Metastatic sites	
Liver	16 (67)
Lymph nodes	13 (54)
Peritoneal seeding	6 (25)
Lung	4 (17)
Bone	2 (8)
Patients with $\geq 1$ surgical intervention	14 (60)

### Efficacy

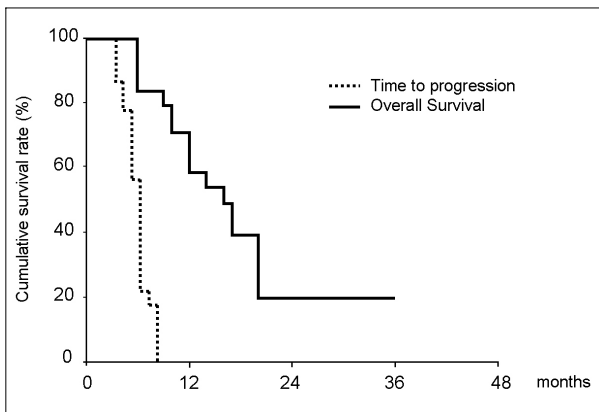
Eight of the 24 patients (33%, 95% CI, 19-48%) had a partial response (PR) and ten patients (42%) had stable disease (SD) (investigator-determined responses, Table 2). The median TTP was 6.0 months (95% CI, 3.0-8.1 months), and the median overall survival was 16 months (95% CI, 13.8-18.3 months). The 1-year actuarial survival rate was 58% (Fig. 1). Efficacy data are shown in Table 2.

**Table 2.** Efficacy Data

Evaluable factors	No. (%)	95% CI (%)
Response (investigators)		
Complete response (CR)	0 (0)	
Partial response (PR)	8 (33)	19 - 48
Stable disease (SD)	10 (42)	
Progressive disease (PD)	6 (25)	
Response rate (CR + PR)	8 (33)	19 - 48
Median TTP (months)	6	3.8 - 8.1
Median OS (months)	16	13.8 - 18.3

\*RECIST criteria.

TTP, time to progression; OS, overall survival.



**Fig. 1.** The median TTP was 6.0 months (95% CI, 3.0-8.1 months), and the median overall survival was 16 months (95% CI, 13.8-18.3 months). The 1-year actuarial survival rate was 58%.

**Safety**

Table 3 summarizes the toxicity observations. Non-hematological adverse events (Grade 2 percentage/Grade 3 percentage) were: nausea (25%/8%), hand-foot syndrome (17%/8%), general weakness (17%/8%), anorexia (17%/4%), stomatitis (13%/4%), vomiting (13%/4%), constipation (4%/4%), and diarrhea (4%/4%). Grade 3 neutropenia, anemia, and thrombocytopenia occurred

in 13%, 8% and 8% of patients, respectively. Two patients developed febrile episodes. Grade 2 and Grade 3 hepatotoxicity developed in 8% and 8% of patients, respectively. No Grade 4 toxicity was seen. No patient discontinued treatment because of abnormal laboratory values. No deaths attributed to toxicity occurred during the study. There were 13 deaths reported during the study, the majority of which occurred more than 28 days after the end of the planned treatment schedule. All of the deaths were related to disease progression.

**DISCUSSION**

A modest response was observed in the current Phase II study of CapGem combination chemotherapy for patients with locally advanced or metastatic GBC. The drug combination was generally well-tolerated. Overall, there were eight confirmed partial responses (PR) observed, with an estimated PR rate of 33% (95% CI, 19-48%). This compares with published PR rates of 16-30% reported for the use of gemcitabine alone.<sup>8,19</sup> The median survival in our trial was 16 months, which is better than the 6.5-11.5 months in the single-

**Table 3.** Toxicities of Chemotherapy (N=24)

Toxicity (NCI-CTC)	Grade 1-2 (%)	Grade 3 (%)	Grade 4
<b>Hematologic</b>			
Neutropenia	4 (17)	3 (13)	-
Anemia	4 (17)	2 (8)	-
Thrombocytopenia	3 (13)	2 (8)	-
<b>Nonhematologic</b>			
Nausea	6 (25)	2 (8)	-
HFS*	4 (17)	2 (8)	-
General weakness	4 (17)	2 (8)	-
Anorexia	4 (17)	1 (4)	-
Stomatitis	3 (13)	1 (4)	-
Vomiting	3 (13)	1 (4)	-
Constipation	1 (4)	1 (4)	-
Diarrhea	1 (4)	1 (4)	-
<b>Hepatic</b>			
AST/ALT elevation	1 (4)	1 (4)	-
Bilirubin elevation	1 (4)	1 (4)	-

\*HFS, hand-foot syndrome.

agent gemcitabine trials. The combination of capecitabine and gemcitabine, based on the dose and schedule as used in our trial, has better activity than gemcitabine alone. It is possible that capecitabine may enhance the activity of the combination. In a recent single-arm study of oral capecitabine therapy, a 50% treatment response was reported in patients with GBC.<sup>20</sup> Further, in an interim report of a trial using capecitabine and gemcitabine, five of 15 patients with biliary tract cancers achieved a PR.<sup>21</sup> These results suggest that capecitabine and gemcitabine may be a reasonable treatment combination for biliary tract cancers, including GBC. In human tumor xenograft models, oral administration of capecitabine yielded substantially higher concentrations of 5-FU in tumor specimens than in specimens of plasma or normal tissue. It is noteworthy that levels of 5-FU after administration of capecitabine were much higher than those achieved by IV administration of 5-FU at doses producing equal levels of toxicity. The susceptibility of the xenografts to capecitabine was correlated with levels of the enzyme thymidine phosphorylase in tumor tissue specimens. Therefore, the efficacy of capecitabine may be optimized by selecting candidates for treatment on the basis of thymidine phosphorylase expression or by combining this agent with other agents that can upregulate thymidine phosphorylase expression within tumor tissue.<sup>15,16</sup>

Phase II trials of approximately 130 patients treated with a chemotherapy regimen of gemcitabine in combination with other agents show response rates ranging from 9 to 53%, with a tolerable toxicity profile.<sup>22-27</sup> Overall survival in these studies ranged from 6.3 to 16 months. Most of these studies have included all biliary tract cancers. A recent Phase II study using the combination of gemcitabine and cisplatin in advanced GBC has reported high activity (64% response rate) with a tolerable toxicity profile.<sup>28</sup> The present data and literature review, however, do not address the question whether this combination is superior or equivalent to single-agent gemcitabine or CapGem combination. Thus, further confirmative Phase III trials will be needed.

Nausea and hand-foot syndrome were the most common side effects of treatment, and hematologic toxicity was limited to Grades 2 and 3. The

mildness of the observed toxicity may be attributable to the less aggressive starting dose of capecitabine (1,000 mg/m<sup>2</sup>) used for this group of patients. The use of 1,000 mg/m<sup>2</sup> capecitabine has become common in the treatment of patients with other malignancies, such as colorectal carcinoma; this reduced dose was suggested by Borner et al.,<sup>29</sup> who also recommended the use of 1,000 mg/m<sup>2</sup> twice daily when capecitabine is used in combination with oxaliplatin. Although impaired hepatic function can exacerbate toxicity or inhibit the efficacy of many agents, the presence of mild-to-moderate hepatic dysfunction had no clinically significant effect on the pharmacokinetics of capecitabine and its metabolites.<sup>17</sup> This finding suggests that the CapGem regimen may be useful for patients with hepatobiliary carcinoma, including patients with mildly-to-moderately impaired hepatic function.

Further research in this area should be directed at finding the best cytotoxic agent for combination with capecitabine or gemcitabine, or altering the dose intensity or route of administration in advanced gallbladder cancer. A larger trial of gemcitabine combined with cisplatin compared with CapGem needs to be conducted. Also, the role of the CapGem combination as an adjuvant treatment for suboptimally resected patients should be further pursued.

## REFERENCES

1. Verderame F, Mandina P, Abruzzo F, Scarpulla M, Di Leo R. Biliary tract cancer: our experience with gemcitabine treatment. *Anticancer Drugs* 2000;11:707-8.
2. Murakami K, Tanimura H, Yamaue H, Mizobata S, Noguchi K, Nakamori M, et al. Clinical effect of immunochemotherapy for a patient with advanced gallbladder cancer: report of a case. *Surg Today* 1998;28:923-8.
3. Hasegawa H, Ueo H, Nanbara S, Tsuji K, Mori M, Akiyoshi T. An effective pre-operative chemoimmunotherapy regimen against advanced gallbladder carcinoma: a case report. *Hepatogastroenterology* 1999;46:1639-42.
4. Hara Y, Kawasaki T, Yabata E, Gen T, Jibiki M, Kudoh A, et al. A case of unresectable gallbladder cancer responding to combination therapy with hyperthermia and local chemotherapy. *Jpn J Cancer Chemother* 2000;27:117-20.
5. Makower D, Rozenblit A, Kaufman H, Edelman M,

- Lane ME, Zwiebel J, et al. Phase II clinical trial of intralesional administration of the oncolytic adenovirus ONYX-015 in patients with hepatobiliary tumors with correlative p53 studies. *Clin Cancer Res* 2003;9:693-702.
6. Gallardo J, Fodor M, Gamargo C, Orlandi L. Efficacy of gemcitabine in the treatment of patients with gallbladder carcinoma: a case report. *Cancer* 1998;83:2419-21.
  7. Castro MP. Efficacy of gemcitabine in the treatment of patients with gallbladder carcinoma: a case report. *Cancer* 1998;82:639-41.
  8. Gallardo JO, Rubio B, Fodor M, Orlandi L, Yanez M, Gamargo C, et al. A phase II study of gemcitabine in gallbladder carcinoma. *Ann Oncol* 2001;12:1403-36.
  9. Raderer M, Hejna MH, Valencak JB, Kornek GV, Weinlander GS, Barek E, et al. Two consecutive phase II studies of 5-fluorouracil/leucovorin/mitomycin C and of gemcitabine in patients with advanced biliary cancer. *Oncology* 1999;56:177-80.
  10. Penz M, Kornek GV, Raderer M, Ulrich-Pur H, Fiebigler W, Lenauer A, et al. Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. *Ann Oncol* 2001;12:183-6.
  11. Bruckner HW, Zhou G, Haenel P. *Ex vivo* ATP tumor testing of gemcitabine for combination chemotherapy and biochemical modulation. *Proc Am Assoc Cancer Res* 1998;39:310.
  12. Poplin E, Roberts J, Tombs M, Grant S, Rubin E. Leucovorin, 5-fluorouracil, and gemcitabine: a phase I study. *Invest New Drugs* 1999;17:57-62.
  13. Hidalgo M, Castellano D, Paz-Ares L, Gravalos C, Diaz-Puente M, Hitt R, et al. Phase I-II study of gemcitabine and fluorouracil as a continuous infusion in patients with pancreatic cancer. *J Clin Oncol* 1999;17:585-92.
  14. Schuller J, Cassidy J, Dumont E, Roos B, Durston S, Banken L, et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. *Cancer Chemother Pharmacol* 2000;45:291-7.
  15. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, 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;34:1274-81.
  16. Endo M, Miwa M, Eda H, Ura M, Tanimura H, Ishikawa T, et al. Induction of thymidine phosphorylase expression and enhancement of efficacy of capecitabine or 5-deoxy-5-fluorouridine by cyclophosphamide in mammary tumor models. *Int J Cancer* 1999;83:127-34.
  17. Twelves C, Glynne-Jones R, Cassidy J, Schuller J, Goggin T, Roos B, et al. Effect of hepatic dysfunction due to liver metastases on the pharmacokinetics of capecitabine and its metabolites. *Clin Cancer Res* 1999;5:1696-702.
  18. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized Phase III study. *J Clin Oncol* 2001;19:2282-92.
  19. Rudi J. Chemotherapy with gemcitabine in patients with gall-bladder carcinoma. *Ann Oncol* 2002;13:807.
  20. Patt YZ, Hassan MM, Aguayo A, Nooka AK, Lozano RD, Curley SA, et al. Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. *Cancer* 2004;101:578-86.
  21. Knox JJ, Hedley D, Oza A, Siu E, Chen R, Feld M, et al. Phase II trial of gemcitabine plus capecitabine (GemCap) in patients with advanced or metastatic adenocarcinoma of the biliary tract. *Proc Am Soc Clin Oncol* 2003;22:317.
  22. Carraro S, Servenio PJ, Bruno MF, Castillo Odena MDS, Roca E, Jovtis S, et al. Gemcitabine and cisplatin in locally advanced or metastatic gallbladder and bile duct adenocarcinomas. *Proc Am Soc Clin Oncol* 2001;20:A2333.
  23. Gebbia V, Giuliani F, Maiello E, Colucci G, Verderame F, Borsellino N, et al. Treatment of inoperable and/or metastatic biliary tree carcinomas with single agent gemcitabine or in combination with levoleinic acid and infusional fluorouracil: results of a multicenter phase II study. *J Clin Oncol* 2001;19:4089-91.
  24. Kuhn R, Ridwelski K, Eichelmann K, Rudolph S, Fahlke J, Ridwelski K. Outpatient combination chemotherapy with gemcitabine and docetaxel in patients (Pts) with cancer of the biliary system. *Proc Am Soc Clin Oncol* 2001;20:A2272.
  25. Kornek GV, Schuell B, Laengle F, Gruenberger T, Penz M, Karall K, et al. Mitomycin C in combination with capecitabine or biweekly high dose gemcitabine in patients with advanced biliary tract cancer: a randomized phase II trial. *Ann Oncol* 2004;15:478-83.
  26. Scheithauer W. Review of gemcitabine in biliary tract carcinoma. *Semin Oncol* 2002;29:40-5.
  27. Murad AM, Guimara RC, Aragao BC, Rodrigues VH, Scalabrini-Neto AO, Padua CA, et al. Phase II trial of the use of gemcitabine and 5-fluorouracil in the treatment of advanced pancreatic and biliary tract cancer. *Am J Clin Oncol* 2003;26:151-4.
  28. Malik IA, Aziz Z, Zaidi SHM, Sethuraman G. Gemcitabine and cisplatin is a highly effective combination chemotherapy in patients with advanced cancer of the gall bladder. *Am J Clin Oncol* 2003;26:174-7.
  29. Borner MM, Dietrich D, Stupp R, Morant R, Honegger H, Wernli M, et al. Phase II study of capecitabine and oxaliplatin in first- and second-line treatment of advanced or metastatic colorectal cancer. *J Clin Oncol* 2002;20:1759-66.