석 사 학 위 논 문

Treatment Efficacy and Toxicity of Targeted Combination Therapy in Elderly Patients with Colon Cancer

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이 논문을 석사학위 논문으로 제출함

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사랑합니다.

2022년 8월

김 현 지

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1. Introduction

Colon cancer is one of the most common cancers in western countries (1) and the third common cancer in Korea (2). The basic treatment for colon cancer was fluorouracil based combination chemotherapy, which showed poor prognosis in metastatic colon cancer (3). However, recently, the progression free survival (PFS) and overall survival (OS) have been improved encouragingly when triple combination chemotherapy was performed, including targeted treatments such as cetuximab and bevacizumab (3,4). Most clinical studies target relatively young and fit patients under the age of 70 and it is difficult to represent the recently increasing elderly population (5,6). The elderly population is growing and age has a great influence on treatment decisions. It is known that elderly patients usually have poor performance and are more sensitive to drug toxicity (7). However, the age cannot be considered the only parameter in medical practice. As mentioned above, it is urgent to analyze the actual reaction and toxicity of anticancer drugs of elderly patients. This study was conducted in order to evaluate the response rate, PFS, OS, safety and prognostic factors of targeted combination chemotherapy in colon cancer patients older than 65 years.

2. Materials and Methods

2.1. Study populations and methods:

We retrospectively analyzed the medical records of 69 patients. Patients were treated at Keimyung university dongsan hospital between January 2007 and July 2017. Patients were enrolled histopathologically confirmed as having metastatic colon cancer with adenocarcinoma according to the World Health Organization classification and only those diagnosed at the age of 65 years or above were considered for the study. Inclusion criteria were no prior palliative chemotherapy, at least 1 cycle of targeted agent (cetuximab or bevacizumab) and patients had radiographically at least one measurable lesion per response evaluation criteria in solid tumors (RECIST) guideline version 1.1. The other eligible criteria were adequate hematological (neutrophile counts ≥ 1,500 /㎣, platelets ≥ 100,000 /㎣, hemoglobin ≥ 9.0 g/dL), kidney (creatinine ≤ 1.5 mg/dL), liver (total bilirubin ≤ 1.5 × upper limit of the normal (ULN), AST and ALT ≤ 3.0 × ULN) functions. Patients were excluded if they had a history of malignancy other than colon cancer, adjuvant chemotherapy within 6 months before first chemotherapy, and operation or radiotherapy within 30 days before first chemotherapy. Medical records were collected for the following characteristics: age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), Charlson comorbidity index (CCI), sideness, disease progression, toxicity, date of last visit, death, chemotherapy drug dosage, chemotherapy cycles, and date of chemotherapy. This study was approved by the institutional review board of Keimyung university dongsan hospital (DSMC

2022-03-072).

2.2. Statistical analyses:

The primary endpoint was objective tumor response rate and secondary endpoints included PFS, OS and safety. PFS and OS were defined as the times from diagnosed as metastatic colon cancer to first documented objective tumor progression or death from any cause, respectively. PFS and OS analysis were evaluated using the Kaplan-Meier method. Categorical variables were compared using X^2, two-sided p values of less than 0.05 and 95% confidence intervals (CIs) were calculated. All analysis were performed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patients' characteristics:

The characteristics of the 69 patients are shown in Table 1. The median age was 73 years (range, 65 – 87 years), with 49 males and 20 females. Most of the patients (87%) had an ECOG PS 1, and CCI usually had the largest number of patients from 0 to 1. Thirty three patients had right side colon cancer, 32 were left, 2 were transverse and the rest of 2 patients were multiple primary sites (ascending, transverse, hepatic flexure and sigmoid colon). Bevacizumab was administered to 42 patients (60.9%) and cetuximab was administered to 27 patients (39.1%). Most patients (89.9%) received targeted agent combined with FOLFIRI regimen and others (10.1%) received FOLFOX regimen. Bevacizumab plus FOLFIRI was administerd to 35 patients (8.2 cycles), bevacizumab plus FOLFOX was 7 patients (6.8 cycles) and cetuximab plus FOLFIRI was 27 patients (7.2 cycles). Mean cycles of combined chemotherapy were 7.4.

3.2. Efficacy:

Complete response was 9 (13.1%), partial response was 23 (33.3%) and progressive disease was 9 (13.0%) patients. Overall response rate was 46.4% and disease control rate was 62.3%. The response characteristics are shown in Table 2. The median PFS was 10.0 months (95% CI: 6.8 – 13.2) (Figure 1). The median OS was 26.0 months (95% CI: 11.6 – 40.4) (Figure 2).

3.3. Toxicity:

Adverse events were reported by using NCI Common Terminology Criteria for Adverse Events 4.0 (CTCAE 4.0). Safety data were reviewed by investigators based on electronic medical records. The adverse events that occurred during this study are summarized in Table 3. For hematological toxicity, grade 3/4 neutropenia occurred in 13 patients (18.8%)/27 patients (39.1%). Grade 2 neutropenia occurred in 7 patients (10.1%). Among them, 18 patients were performed dose adjustment in case of grade 4 neutropenia, and they received granulocyte colony-stimulating factor (G-CSF) with nutritional support. No patient was withdrawal because of neutropenia. From the next cycle, the patients who experienced grade 4 neutropenia were received preventive G-CSF. Only 2 patients were fell into grade 3 neutropenia again and they experienced 1 level dose reduction after first neutropenia event. Febrile neutropenia developed in 13 patients (18.8%). The most common hematologic side effects was anemia with grade 1/2 in 24 patients (34.8%)/26 patients (37.7%). Non-hematological toxicities were generally mild and manageable. The most common non-hematological toxicity were nausea, diarrhea, fatigue, and thromboembolic event. Grade 2 nausea was observed in 5 patient. The most common grade 3/4 toxicities were thromboembolic events. Thrombosis occurred in popliteal vein, peroneal vein, common femoral vein, soleal vein and was cured with dalteparin. The second common grade 3/4 toxicities were nausea and vomiting but most cases were manageable with antiemetic drugs (5-hydroxytryptamine typer 3 receptor antagonist, neurokinin-1 receptor antagonist, dexamethasone, and metoclopropamide). The third most common grade 3/4 non-hematologic toxicities were diarrhea, five

patients experienced diarrhea and they recovered after hydration and supportive care. Only one patient received 1 level dose reduction. Diarrhea was mostly caused by irinotecan, and anti-diarrheal drugs were prophylactically given. Four patients discontinued chemotherapy due to toxicity (grade 2/3 fatigue, grade 3 delirium, and grade 4 colon perforation). The patient who experienced colon perforation recovered after surgical treatment and he refused treatment because of poor performance. There were two treatment related mortality. One patient with bevacizumab experienced grade 5 colon perforation and the other patient visited hospital because of sudden cardiac arrest with unknown cause.

Table 1. Patient Characteristics

Characteristics	Number of patients (n = 69) (%)
Age (years)	
Median (range)	73 (65 - 87)
Male/female	49 (71.0)/20 (29.0)
ECOG PS**	
0	0 (0.0)
1	60 (87.0)
2	9 (13.0)
CCI*	
0	36 (52.2)
1	16 (23.2)
2	8 (11.6)
3	7 (10.1)
4	1 (1.4)
5	0 (0.0)
6	1 (1.4)
Sideness	
Right	33 (47.8)
Transverse	2 (2.9)
Left	32 (46.4)
Multiple	2 (2.9)
Target agent	
Bevacizumab	42 (60.9)
Cetuximab	27 (39.1)
Systemic chemotherapy	
FOLFOX	7 (10.1)
FOLFIRI	62 (89.9)

* CCI, Charlson comorbidity index; ** ECOG PS, Eastern Cooperative Oncology Group performance score.

Table 2. Objective Tumor Response Rates

Best objective response	Number (n = 69) (%)
Complete response	9 (13.1)
Partial response	23 (33.3)
Stable disease	11 (15.9)
Progressive disease	9 (13.0)
Overall response rate	46.4%
Disease control rate	62.3%

Table 3A. Toxicity Profiles

	Grade (Number of patients) (n = 69)			
	1	2	3	4
Hematologic				
Neutropenia	0 (0.0)	7 (10.1)	13 (18.8)	27 (39.1)
Febrile neutropenia	0 (0.0)	8 (11.6)	1 (1.4)	4 (5.8)
Anemia	24 (34.8)	26 (37.7)	14 (20.3)	0 (0.0)
Thrombocytopenia	8 (11.6)	2 (2.9)	3 (2.9)	2 (2.9)

Table 3B. Toxicity Profiles (continued)

	Grade (Number of patients) (n = 69)				
	1	2	3	4	5
Non-hematologic					
Nausea	4	5	4	0	0
Diarrhea	4	2	5	0	0
Fatigue	0	8	3	0	0
Vomiting	2	2	5	1	0
Thromboembolic event	0	1	7	1	0
Rash	3	2	1	0	0
Abdominal pain	1	3	1	0	0
Infusion related reaction	0	4	0	0	0
Constipation	3	1	0	0	0
Ileus	0	1	1	0	0
Oral mucositis	1	1	0	0	0
Colon perforation	0	0	0	1	1
Peripheral sensory neuropathy	1	1	0	0	0
Hypertension	0	2	0	0	0
Cardiac arrest	0	0	0	1	1
ALT* elevation	1	1	0	0	0
AST** elevation	3	1	0	0	0
Acute kidney injury	1	0	0	0	0
Insomnia	2	0	0	0	0
Acute coronary syndrome	0	0	1	0	0
Anxiety	1	0	0	0	0
Cognitive disturbance	1	0	0	0	0
Delirium	0	0	1	0	0
Infusion site extravasation	0	1	0	0	0

* ALT, alanine aminotransferase; ** AST, aspartate aminotransferase.

Table 4. Drug Administration

	Mean cycle (range)	Mean dose % (range)
Cetuximab	7 (1 - 20)	97.8 (75 - 100)
Bevacizumab	7.8 (1 - 22)	97.4 (75 - 100)
5-fluorouracil	7.6 (1 - 22)	94.7 (60 - 100)
Oxaliplatin	6.8 (1 - 11)	93.5 (80 - 100)
Irinotecan	7.6 (1 - 22)	95.0 (60 - 100)

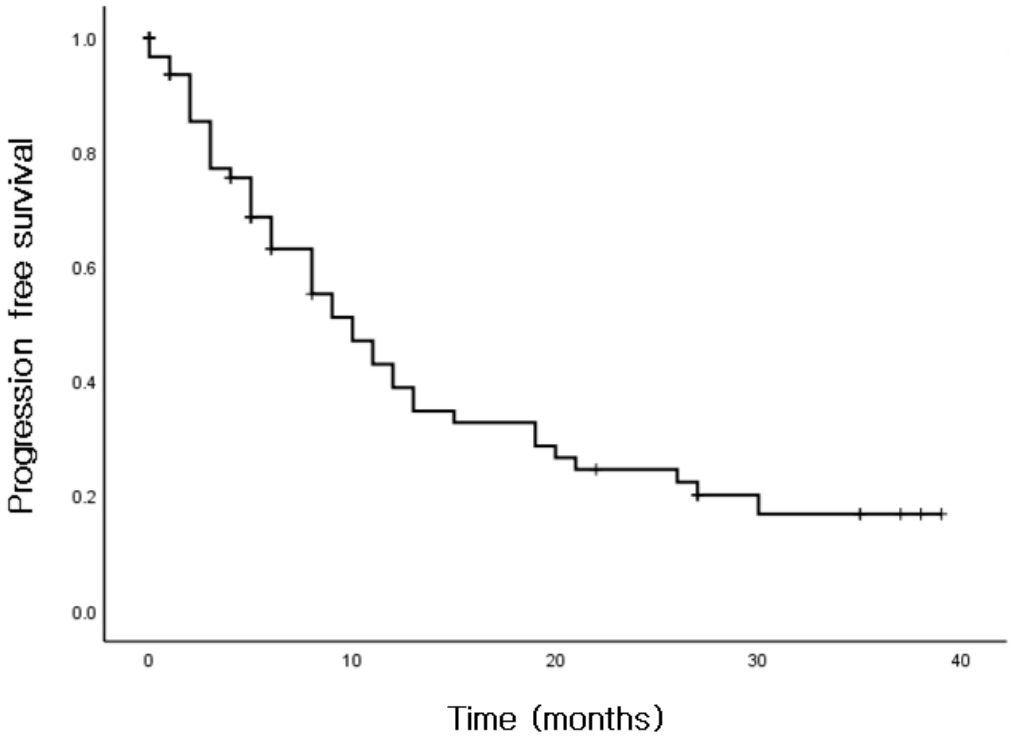

Figure 1. Progression frees survival in elderly patients with metastatic colon cancer. The median survival time was 10.0 months (95% CI: 6.8 - 13.2).

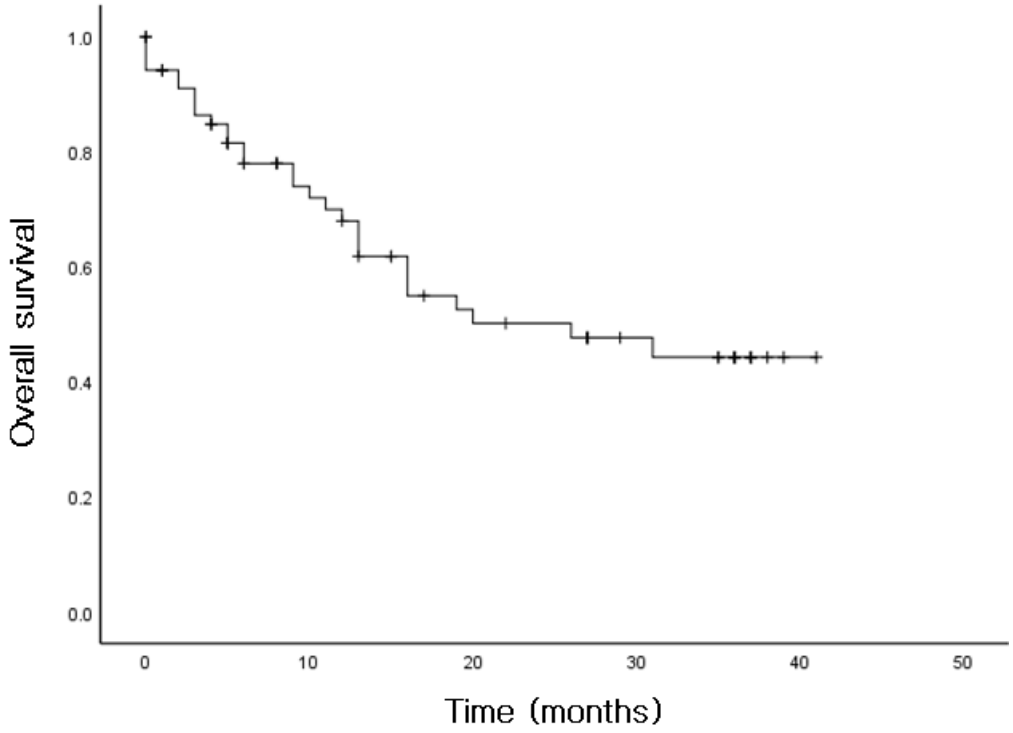

Figure 2. Overall survival in elderly patients with metastatic colon cancer. The median survival time was 26.0 months (95% CI: 11.6 - 40.4).

4. Discussion

Physicians sometimes hesitated to treat elderly metastatic colon cancer patients with standard full dose combination chemotherapy with targeted therapy because of inadequate data about the benefit-risk ratio of these regimens in elderly patients (8). We have limited data about results of elderly metastatic colon cancer with targeted therapy, in particulary above 65 years (9,10). Retrospective pooled analysis data showed that bevacizumab combination chemotherapy in elderly patients have similar PFS and OS compared with below 65 years old patients (11). Many studies proved clinical benefits with combination chemotherapy but most studies excluded elderly patients with poor performance status or comorbidities so the results may not represent to the real world data (12). Elderly patients have received less aggressive treatment and have shorter treatment period in real clinical practice. We are actually influenced by patients age, age associated characteristics and comorbidities to make treatment decision, which could affect PFS and OS in metastatic colon cancer patients. In the FIRE-3 study, the combined treatment of cetuximab and FOLFIRI was compared with the combined treatment of bevacizumab and FOLFIRI, and the median PFS was 10.0 months (95% CI: 8.8 - 10.8) in the cetuximab group and 10.3 months (95% CI: 9.8 - 11.3) in the bevacizumab group (13). And median OS was 28.7 months (95% CI: 24.0 - 36.6) in the cetuximab group compared with 25.0 months (95% CI: 22.7 - 27.6) in the bevacizumab group (14). Our this retrospective data showed non-inferior median PFS (10.0 months, 95% CI: 6.8 - 13.2) and OS (26.0 months, 95% CI: 11.0 - 40.4) compared with prior representative data (13,14). This data was real world data and included patients with poor

performance and comorbidities. Usually, the rates of chemotherapy associated adverse events in the eldery patient were higher to rates in the younger patients (< 65 years) (9). However triplet regimen including cetuximab or bevacizumab (especially bevacizumab) could increase adverse events including thromboembolic events, gastrointestinal perforation, bleeding, would healing complication, uncontrolled hypertension, diarrhea and skin toxicities (9,10,15). From the toxicological point of view, the dose was reduced, but it is thought that management is necessary because the number of patient rejections is the highest. Eldery patients are suffer from frequent hospital visit due to complication of chemotherapy. They need support of caregivers. As such, social support is urgently needed. Actually, social support is important, as Sindhuja Kadambi et al. (16) addressed that, “Older adults with cancer have significant physical, emotional, informational, practical, and medical support needs”. The results of the toxicity profile showed that neutropenia was the most characteristic. Appropriate preventive G-CSF use is required to prevent neutropenia. In elderly patients with colon cancer, clinical outcomes showed similar results compared with prior clinical trials (13,14). Grade 4 hematologic adverse events were higher than prior study results. Clinicians should be caution in caring for elderly patients especially in hematologic adverse events. In clinical practice, the use of targeted agent combination therapy can be of great benefit to survival rates. It seems that managing these toxicity well to prevent complications will help improve survival rates. Reflecting the increasing number of elderly patients, it is expected that active supportive care during chemotherapy will help improve survival rate. In the bevacizumab plus FOLFOX group, two patients started dose reduction in consideration of their elderly age. Both patients were administered up to 11 cycles, and it was not a bad result compared to

the average cycle of the therapy. Therefore, there was a survival benefit if well overcome with dose reduction and appropriate treatment and management.

5. Summary

In elderly metastatic colon cancer patients, the treatment results of combination therapy with targeted treatment showed similar results to those reported in clinical trials with median PFS 10.0 months and OS 26.0 months. Overall response rate was 46.4% and disease control rate was 62.3%. Attention to grade 3/4 neutropenia, thromboembolic events, and colon perforation in the treatment of elderly metastatic colon cancer patients is required.

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Treatment Efficacy and Toxicity of Targeted Combination Therapy in Elderly Patients with Colon Cancer

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(Abstract)

Elderly cancer patients usually have poor performance and are more sensitive to drug toxicity. Most clinical studies target relatively young and fit patients under the age of 70 and it is difficult to represent the recently increasing elderly population. Therefore, this study was conducted in order to evaluate the response rate, progression free survival (PFS), overall survival (OS), safety and prognostic factors of targeted combination chemotherapy in colon cancer patients older than 65 years. This retrospective study included 69 elderly patients with metastatic colon cancer who have not received palliative chemotherapy before. All patients were histologically confirmed colon cancer from

January 2007 to July 2017. All recruited patients received either cetuximab or bevacizumab with combination chemotherapy every 2 weeks. The median age was 73 (range 65 - 87). Bevacizumab was administerd to 42 patients (60.9%) and cetuximab was administered to 27 patients (39.1%). The most common hematologic side effect was anemia. Systemic chemotherapy with targeted agents were moderately tolerated with grade 3/4 neutropenia to 40 patients. Non-hematological side effects to watch out for were thromboembolic event and colon perforation. Overall response rate was 46.4% and disease control rate was 62.3%. In elderly metastatic colon cancer patients, the treatment results of combination therapy with targeted treatment showed similar results to those reported in clinical trials with median PFS 10.0 months (95% CI: 6.8 - 13.2) and OS 26.0 months (95% CI: 11.6 - 40.4).

고령의 대장암 환자에서 표적치료제 병용요법의 치료 유효성과 독성

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(초록)

고령의 암 환자는 동반 질환과 낮은 수행력과 연관하여 항암치료제 독성에 더 민감한 것으로 알려져 있다. 대부분의 임상연구는 70세 이하의 비교적 젊은 성인을 대상으로 하고 있어 최근 증가하는 노령 인구를 대표하기 어렵다. 따라서 본 연구는 65세 이상 고령의 대장암 환자에서 표적치료제 병용요법의 반응률, 무진행 생존율과 안정성 및 예후 인자를 평가하고자 하였다. 2007년 1월부터 2017년 7월 사이에 조직학적으로 대장암을 진단받은 이후 첫 치료로 2주마다 cetuximab 또는 bevacizumab을 포함한 항암치료를 받은 65세 이상의 환자 69명을 후향적으로 분석하였다. 평균 나이는 73세였고, bevacizumab을 투여한 환자는 42명(60.9%), cetuximab을 투여한 환자는 27명(39.1%)이었다. 가장 흔한 혈액학적 부작용은 빈혈이었고 40명의 환자에서 3/4등급 호중구 감소증이 발생하였다. 주의해야 할 비 혈액학적 부작용은 혈전과 대장 천공이었다. 객관적 반응률은 46.4%였고 질병 조

절률은 62.3%이였다. 고령의 대장암 환자에서 표적치료제 병용요법의 치료 결과가 무진행생존율 10.0 개월(95% CI: 6.8 – 13.2), 전체생존율 26.0 개월 (95% CI: 11.6 – 40.4)로 임상시험에서 보고하는 것과 유사한 결과를 보였다.