

## Bevacizumab (Bmab) +Dihydropyrimidine Dehydrogenase (DPD) Inhibitory Fluor pyrimidine (DIF) Combined Chemotherapy for the Treatment of Late-Stage Elderly Patients with Advanced/Recurrent Colorectal Cancer (ARCC)

Kazuma Kobayashi

Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences 1 -7-1 Sakamoto, Nagasaki City, Nagasaki 852-8501, Japan

### Abstract

**Objective:** In Japan, the elderly represent more than 20% of the total population. The incidence of elderly patients with advanced/recurrent colorectal cancer (ARCC) has also increased. However, the optimal regimen for elderly patients, particularly those over 75 years of age (advanced elderly), has not been established.

**Results:** The STD was 979 days, the median PFS was 350 days, and the RR was 23.3%. Grade  $\geq 3$  AEs with each regimen were: Bob + DIF, 1.9%, other regimens, 14.4%. Although no significant difference was observed in OS or PFS between Bmab + DIF and other treatment regimens, the transition rate to 2nd line chemotherapy after disease progression after first-line treatment was higher with Bmab + DIF (54.6% [6/11]) than with other treatment regimens (38.9% [7/18]); however, this difference did not reach statistical significance.

### Keywords

Elderly patient; colorectal cancer; Bevacizumab; DIF

### Introduction

The United Nations and the World Health Organization define people between the ages of 65 and 75 as early-stage people; people aged 75 to 89 as older adults; and people over the age of 90 as hyper-stage seniors. The ratio of elderly people in a society is used to define its level of aging. An aging society is defined by a ratio of 7-14%, an aging society is defined by a ratio of 14-21% and a hyper-aging society is defined by a ratio  $\geq$  of 21%. According to these definitions, Japan, which had a ratio of 24.2% in 2012, is defined as a hyper-aged society. Currently, the elderly population is increasing. Since the ASCO2012 presentation of the AVEX trial, Bevacizumab (Bmab) + capecitabine has been widely used as a first-line treatment for elderly patients with advanced and recurrent colorectal cancer (ARCC) [2]. It is also a standard chemotherapy regimen for patients who are not eligible for intensive treatment according to the 2014 guidelines for the treatment of colorectal cancer [3]. However, it is associated with a high incidence of hand-foot syndrome ( $> 50\%$ ) and a lower quality of life (QoL) in patients with grade 3/4 colorectal cancer [2]. In Japan, UZEL / UFT (tegafur/uracil) or S-1 has been widely used for ARCC. These agents are fluoropyrimidines (DIF) which inhibit dihydropyrimidine dehydrogenase (DPD). They consist of tegafur, which is a prodrug of 5-FU, and a DPD inhibitor that inhibits DPD activity. They maintain a high blood concentration of 5-FU and are associated with a decrease.

### Patients and Methods

The present study included elderly chemotherapy-naive advanced patients with ARCC who were treated between January 1996 and October 2014 and who received at least one course of chemotherapy. Patient medical records were reviewed retrospectively to compare the results of chemotherapy with Bmab + DIF and other regimens. The response criteria for solid tumors (RESIST) and the National Cancer Institute (NCI-CTC) version 4.0 common toxicity criteria were used to assess chemotherapy regimens. Median survival time (STD) and median progression-free survival (PFS) were calculated using the Kaplan-Meier

method. Other factors were assessed by Fisher's exact test. Stat View J 5.0 (Abacus Concepts, Stat View. Abacus Concepts, Inc., Berkeley, CA) was used to perform the statistical analyzes. Values of  $p < 0.05$  were considered to indicate a statistically significant difference.

### Discussion

In the present study, we achieved an MST of 979 days and an mPFS of 350 days. This has shown that chemotherapy improves the survival of advanced elderly patients with ARCC. The RR was higher with other regimens than with Bob + DIF. In addition, metastasectomy and radiofrequency ablation (RFA) therapy were performed in two patients with liver metastases who received other regimens. Thus, when targeting conversion therapy, intensive chemotherapy including L-OHP, CPT-11 and targeted molecular agents may be appropriate. Regarding the lack of significant difference in PFS and OS of patients who received Bmab + DIF and those who received other regimens, it was concluded that Bmab + DIF was not the only optimal regimen for advanced elderly patients with ARCC.

### Conclusions

Although we could not confirm a single regimen that was appropriate for the treatment of advanced elderly patients with ARCC, Bmab + DIF was suggested as the treatment of choice due to the 100% disease control rate, good feasibility, and a smooth transition to second-line chemotherapy. Thanks

Any substantial contribution provided by a person different from the author and list all other people who do not meet the authorship criteria. We thank you for the help of medical writing expert Brian Quinn in Japanese medical communication. This study was carried out only by all of the authors' contributions. The results of this study were standard clinical practice covered by national medical insurance, so we receive no funds or financial support.

### References

- Cunningham D, Lang I, Marcuello E, Lorusso V, Ocivirk J, et al. (2013) Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with untreated metastatic colorectal cancer (AVEX): a randomized open-label phase 3 trial. *Lancet Oncol* 14: 1077-1085.
- Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, et al. (2015) 2014 Guidelines from the Japanese Society for Colon and Rectal Cancer (JSCCR) for the treatment of colorectal cancer. *Int J Clin Oncol* 20: 207-239.
- Douillard JY, Hoff PM, Skillings JR, Eisenberg P, Davidson N, et al. (2002) Multicenter phase III study on uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 20: 3605-3616.

[kazuma-k2013@nagasaki-u.ac.jp](mailto:kazuma-k2013@nagasaki-u.ac.jp)