Research Article

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Maintenance Therapy for Elderly Colorectal Cancer Patients with Bevacizumab: Single Center Experience

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ABSTRACT

Background: *Over the past decade, the outcome of treatment with chemotherapy for metastatic colorectal cancer (mCRC) is substantially better, with proven increases survival. However, many patients still suffer significant toxicities, such as peripheral neuropathy. In advanced countries, where most patients with mCRC are older, maintenance therapy is under study with the goal of reducing severe side effects and maintaining quality of life (QOL). Continuation of cytotoxic chemotherapy in the setting of accumulated toxicities is often not feasible, so less toxic drugs are needed over the long-term. Bevacizumab is one option that has low side effects and proven benefit when combined with chemotherapy. This report describes our experience in giving bevacizumab maintenance therapy to 11 older patients with mCRC and reviews maintenance therapy for mCRC.*

Materials and Methods: *Baseline clinical characteristics, pre-specified bevacizumab-related adverse events, and efficacy data were collected from the local patient registry. Approval was provided by the Juntendo University Hospital Institutional Review Board.*

Results: *Eleven patients received maintenance therapy after FOLFOX and/or FOLFIRI regimens for an average of 476 days. Maintenance therapy was instituted due to several side effects from oxaliplatin-based chemotherapy. Side effect included such as peripheral neuropathy and fatigue could reduce during maintenance therapy and get QOL until end stage.*

Conclusions: *Our experience with these 11 patients, demonstrates both prolonged survival as well as maintained QOL. Bevacizumab based maintenance therapy may be considered in elderly patients with mCRC.*

Keywords

Maintenance therapy, Colorectal cancer, Bevacizumab.

Introduction

Cancer incidence is increasing but mortality is decreasing, though cancer is the second leading cause of death in the world [1]. Colorectal cancer (CRC) ranks 3rd in incidence and causes a significant burden in terms of morbidity and mortality [2,3]. Western high cholesterol diets are a well-known risk factor for CRC, and drugs such as aspirin and diets containing fruits and vegetables are often studied in prevention research [4,5]. Japan is included in the group of advanced countries, in which societies are now aging and many elderly CMC cancer patients are receiving therapy. Age is also a significant risk for incidence of CRC [6,7]. Furthermore, elderly populations often have heart, lung and renal function disorders that impact tolerance of treatment, so there is some debate over whether palliative surgery and no/mild chemotherapy can be chosen [7-9].

Over the past decade, the outcome from treatment with chemotherapy for metastatic colorectal cancer (mCRC) has been substantially upgraded due to the ongoing development of new

chemotherapy [1,10]. In addition, much progress has been made in the field of molecularly targeted drugs [11,12]. As a result, mortality is decreasing even though incidence is increasing. In contrast to the progress in survival, QOL is adversely affected due to higher incidence of side effects in older patients. This is especially true of peripheral neuropathy (CIPN) due to oxaliplatin-associated chemotherapy. This is the most frequent cause of discontinuation of a beneficial chemotherapy [13,14].

One way to overcome complete cessation of treatment due to CIPN is to discontinue the oxaliplatin while continuing maintenance therapy. Maintenance therapy was originally established in non-small cell lung cancer wherein the strategy was to achieve prolonged disease stability without worsening the side effects of the initially effective therapy. The strategy is to extend survival and maintain quality of life.

Our hospital is a regional center that cares for community patients, who are often elderly. Here we report our single hospital experience with the use of bevacizumab as maintenance therapy for elderly patients with mCRC. Literature is also reviewed.

Patients and Methods

Baseline clinical characteristics, pre-specified bevacizumab-related adverse events, and efficacy data were collected from the local patient registry from 11 elder patients with mCRC who started bevacizumab-containing chemotherapy in the 1st line setting after receiving oxaliplatin-based treatment. Patients clinical characteristics (primary tumor treatments, and side effects were evaluated. In addition, show 1 case report CT scans and historical table.

Results

Patient characteristics

Eleven elderly patients received maintenance therapy with bevacizumab (Table 1), median age 68 years (62-88); male 61.4%; type of chemo; median duration of chemo etc. Clinical outcomes are shown in Table 2. Most patients received FOLFOX regimen first therapy and FOLFIRI regimen 2nd therapy. The maintenance therapy mean was 476 days with 1 patient receiving almost 2 years survival. Palliative therapy is usually 3 months without any afflictions. Our achievements should go over at least half year survival with quality of life (These 2 sentences belong in the conclusion not the results section).

	Cases
Sex	Man 8　Woman 3
age	mean　72.2(66～84)
Tumor Location	Cecum 1、A/C 2、T/C 1、S/C 1、Rectum 6
Metastasis	Lung 2、Lung and Liver 3、Liver 6
synchronous	6 (lung and liver 3、liver 3)
dyschronous	5 (lung 2、liver 2、dissemination1) After operation mean 491.8 days
K-ras mutation	Wild 1、　mutation 10
Main Side effect for conversing to Maiteance therapy	peripheral neuropathy　5 Fatigue、appetite loss　4 HF syndrome 1 hematocytopenia　1

Table 1: 11 Patients characteristics (make a transition from powerful chemotherapy to maintenance therapy) at baseline.

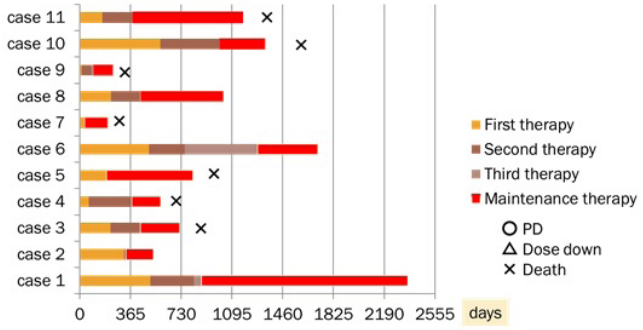


Table 2: 11 Patients therapy outcome.

Table 3 lists the toxicities presents before initiation of maintenance therapy. Fatigue, appetite loss and neuropathy were most common, with neuropathy the main reasons for abandoning chemotherapy. Other side effects included Table 4 shows side effects noted during maintenance therapy with bevacizumab. While no major new problems were apparent, prior oxaliplatin-related toxicities did not change. Table 5 shows all side effects during maintenance therapy. Almost no major side effects appeared until shortly before death.

	All grade	Grade 3≦
Fatigue	5	3
Diarrhea	1	0
Appetite loss	5	3
neuropathy	7	5
Vomit	0	0
hematopenia	3	0
Nausea	1	0
anemia	4	0
Hypertention	0	0
HF syndrome	1	1

Table 3: Side effects before maintenance therapy. Especially fatigue, appetite loss and neuropathy were the reasons for abandoning powerful chemotherapy.

N=11	All grade	Grade 3≦
Side effect caused by Bevacizumab		
proteinuria	0	0
Hypertention	2	0
venous thromboembolism	0	0
arterial thromboembolism	0	0
GI perforation	0	0
Bleeding	1	0
others	0	0

Table 4: Side effects associated by Bevacizumab during maintenance therapy. 11 Patients had no trouble from bevacizumab during long time

therapy.

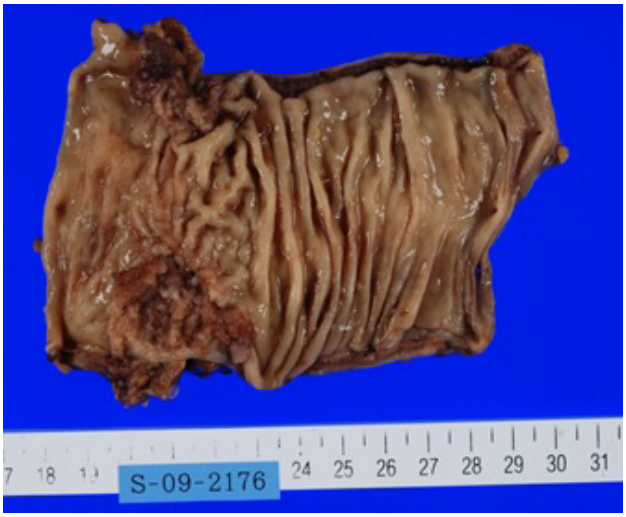
N=11		All grade	Grade 3≦
Side effect caused by Bevacizumab			
Side effect from previous therapy	peripheral neuropathy	7	5
	Fatigue	4	0
stomatitis		1	0
Diarrhea		2	0
hematopenia		1	0
edema		4	0
Appetite loss		2	0
cacogeusia		3	0
anthema		2	0
HF syndrome		5	1

Table 5: All Side effects during maintenance therapy. Almost no major side effect were appeared until shortly before death.

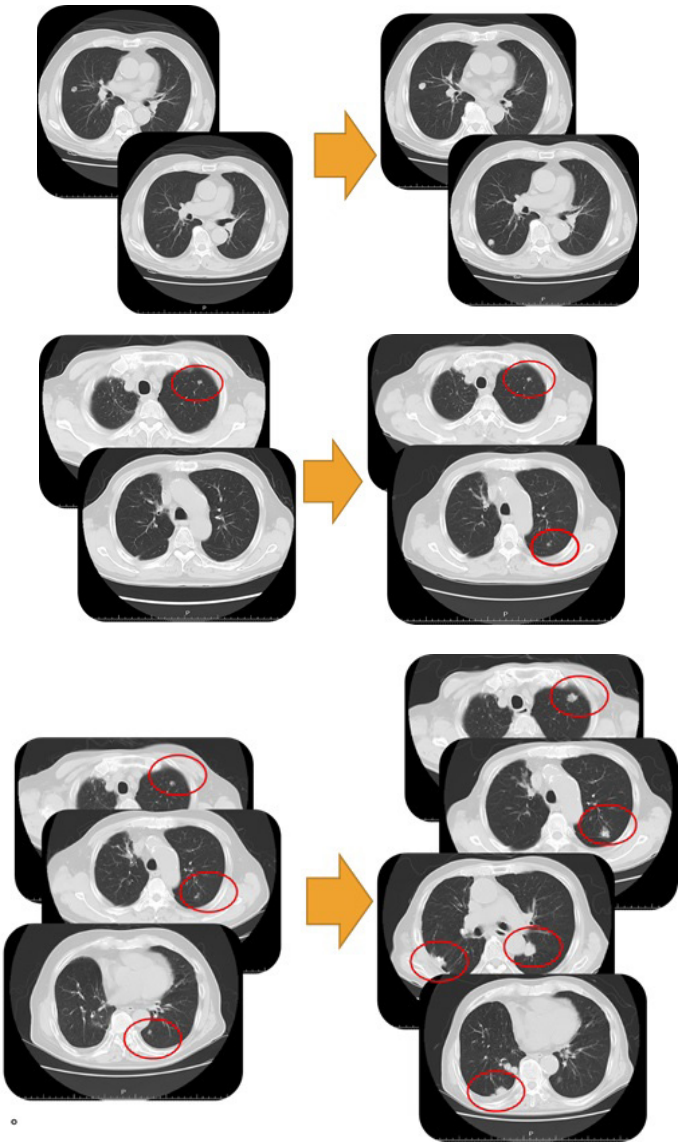
In our hospital 11 patients were able to receive maintenance therapy over an average of 476 days without any major side effects. Some of them could receive treatment at a small clinic near their homes and every 3 months we checked their metastasis status in our hospital. The Japanese government wishes to support medical cooperation between big hospitals and clinics such as this. All patients can stay at home until real end stage without much trouble. We tried to be present with some of them in their houses when they passed away. However, when that patient was in the end stage state, their family gave up their follow up. We need to build out a much better system for home care of maintenance therapy patients, especially in rual areas same as the type of environment around our hospital (Some patients drive up to two hours to get to our hospital). Regarding strong normal chemotherapy, we need to focus on controlling side effects than disease control.

Case Presentation

A 70-year-old man presented with xxx. After staging revealed no systemic metastases, he was treated with low anterior resection with curative intent (Figure1).



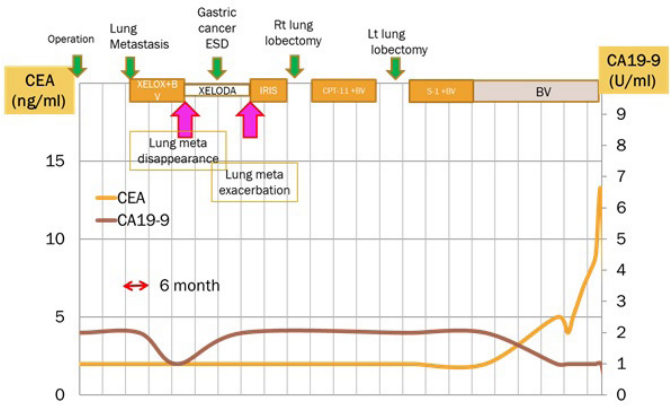
Pathology revealed an R0 resection, type 2, 40×25×20mm, pSS, tub2 Ly2, v1, N(+: 251-1/3, 252-0/1), Ras mutation (+), Stage IIIA. He had OMI history and took DOAC medicine from cardiologist. After a half year on adjuvant oral drug TS-1 treatment, small metastases were found in both lungs with a CT scan (2rt, 1lt). XELOX+BV therapy was started immediately. After one year of well-tolerated treatment the lung metastases resolved and maintenance therapy with BV was initiated. Two right lung metastases were removed, and maintenance therapy continued.



Initially, CPT-11 and beva was started every 2 weeks while checking his side effects. Therapy was occasionally canceled because the patient was experiencing pain in both feet from peripheral occlusive vascular disease and hypocytosis.

After a half year of treatment, two new metastasis were found in the left lung and left lobectomy was performed again. Consequently, a second round of maintenance therapy was started after operation. At that time, his debilitating condition became worse than before, thus only oral chemo drug (UFT/LV) plus beva was taken every

two weeks. He received DIV therapy at a small clinic near his house twice a week for nutritional support during that treatment. This patient could receive maintenance therapy without any major side effects for almost two years. We stopped chemotherapy after he was no longer able to come to the hospital on his own. The patient expired after several months of palliative treatment (Table 6).



Discussion

There are many problems in a graying society; in recent years much has been written about the risk of malignancy [3,6,7,10]. Colorectal cancer (CRC) is a commonly diagnosed cancer and ranks 3rd in incidences for those with a median age of over 70 years [15]. Treatment strategy for older CRC patients may be complicated by certain age-related impairments, philological status, the ability to tolerate treatment toxicity, and much comorbidity [16-18]. More clinical trial evidence is needed before decisions on treatment for older adults can be made [18].

For CRC operations, 70% or more of the cases of laparoscopic surgery can be done even if the patients are elderly and estimation after the operation is the same [19,20], because of minimum invasion, and progressions of operations with material and scopes. 20 years ago, many surgeons chose palliative surgery for curing ileus state, and less LN dissection to prevent major complications. Now advances in science have led to grater longevity for people all over the world.

Elderly patients have heart, lung and renal dysfunctions due to the immune system growing weaker with age [13]. It is usually questions how and where is the goal. By comparing the results in our hospital we found no difference in stage 1 and 2 between old open vs recent laparo surgery in elderly patients, but in stage 3 laparo operations were much better than open (Data not shown). Shiga M and Ho B et al. reviewed the laparoscopic surgery outcomes for elder CRC. They indicated better perioperative outcomes and similar complications with young ages [21,22]. Those results include not only operations, but also adjuvant therapy [23].

Recently, chemotherapy has progressed very quickly. Survival data has changed dramatically for metastatic colorectal cancer (mCRC) [1,10]. Molecularly targeted drugs have done much to support the data, EGFR and VGFR [11,12]. On the other hand, because of severe side effects and graying, there are also many patients suffering from the strategy. Because those results only evaluated the effects of chemotherapy on mCRC, it remains unknown whether elderly patients would benefit from surgery or radiation therapy. Moreover, little is known about clinicopathologic features and prognostic factors specific for this older and frail subset of mCRC patients.

This is especially true of peripheral neuropathy(CIPN), which is based on Oxaliplatin-associated chemotherapy and is the most frequent cause of complete discontinuation of an otherwise successful therapy [13,14].

In general, about 20% of the patients experience grade 3 CIPN and gene dose limiting problems. Those mechanisms reported that oxaliplatin may directly alter axonal voltage-gated sodium channels, inducing an acute neurotoxicity manifested by peripheral nerve hyperexcitability [24,25]. In our data, most patients are giving up on the regular chemotherapy CIPN. Grim J reported high Vitamin D and low saturated fatty acid reduced CIPN complications [26]. Diets for older patients are also 1 of contentable problems. Their metabolisms are also decreasing. Our group has reported low fatty acid leads to chemoprevention and efficacy for chemotherapy [27,28]. Maintaining good metabolic status and nutrient state enables the relinking of low side effect and good chemotherapy results.

In our data, almost all of the elderly patients could not tolerate tough peripheral pneumonitis. We need to think carefully about oxaliplatin induction for older people. If they have some trouble, oncologist could not back to beginning.

Maintence therapy is originally established in non-small cell lung cancer. This treatment strategy is that disease progression control, after the induction of the first effective regimen, is to continue same regimen without toxicity drugs in order to reduce side effects for as long as possible. This concept is that more tolerable toxicity of maintenance approaches leads to ensure a better quality of life.

The strategy of this maintenance (palliative) therapy in oncology is to extend and maintain quality of life for patients with minimum therapy for retarding cancer progression. Our hospital stands in a local area and assumes community healthcare. We manage many elderly colorectal cancer patients. As older patients have less ability to tolerate treatment toxicity, when severe side effects occur they often continue beyond the point of no return. Therefore, the strategy for, and benefits of, cancer treatment for senior patients should not be similar to that of younger patients.

We recommend maintenance therapy with Bevacizumab as another option for elder mCRC.

Bevacizumab is a monoclonal antibody. It is a target for vascular endothelial growth factor (VEGF) receptor which works angiogenesis in cancer growth, and widely standard agents for several tumors [29] and has the possibility of being the root of

maintenance therapy VEGF has been said not only tumoral angiogenesis but also several physiological engaging that involve vascular homeostasis, coagulation, wound healing, renal filtration, and blood pressure regulation. This molecular targeting drug has side effects such as Hypertension (HTN), Proteinuria, bleeding, venous thromboembolism (VTE) and spontaneous perforation of the gastrointestinal tract and so on. Those mechanisms are blocking the repair of damaged endothelial surfaces [30] and leading the ischemia for several organs [31,32].

Bevacizumab effect for the mCRC is sensational and has prolonged survival time much more than before. Most side effects can be managed using drugs but unfortunately there are also side effects, and GI perforation was bleak. I also had some experience with it and stopped not only the treatment, also be home disseminated patients. Nevertheless, we know that these side effects are in very rare cases. Therefore, oncologists should watch for these signs so they can immediately stop and change the strategy. Besides GI perforation, other side effects were not as severe compared with other agents. For maintenance therapy, this drug is very suitable and easy to manage.

Our data also shows that a clinic doctor could do it during outpatient office work. Various social problems such as living alone, no help in the patient's home, living in rural areas, etc, must also be taken into consideration. Our hospital is located in a rural area and many elderly patients are facing problems such as these.

Cancer clinical pass did permit to most suitable chemotherapy near their houses. From the beginning, patients we operated on who were easy to diagnose mCRC in a future, or already have metastasis (mCRC), no treatment, just only observe is very tough decision for oncologist. The results show that maintenance therapy with Bevacizumab is a great option for elderly patients, as it provides 1 year or more prolonged effect without any side effects Ontologically it is now said that immune system disorder and metabolic changes lead to aging quickly.

In the years to come, the research for biomarker of body health, not real age ,goes more further. For example, the immune system and metabolic state will be a great determination factor.

Conclusion

This is a single hospital experience of our present QOL remaining prolonged survival time and the benefit of bevacizumab-based chemotherapy in mCRC 11 for elderly patients. In addition, some patients can received chemotherapy at clinics near their residences, and thus remain at home until real end stage by using clinical PASS between our hospital and clinics. Bevacizumab based maintenance therapy with oral anticancer drug would be optimal for older mCRC patients. We are now shifting UFT/ LV to Trifluridine, Tipiracil Hydrochloride, and new drugs. We will report those data in the future.

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