

Case Series

Open Access, Volume 1

Long survival in metastatic rectal cancer: Due to modulation of the microenvironment?

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Received: Apr 10, 2021

Accepted: May 03, 2021

Published: May 10, 2021

Archived: www.jjgastro.com

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Introduction

The median overall survival time of patients with stage IV rectal cancer is less than 2 years [1]. We present cases of 2 patients with stage IV rectal cancer who survived initial diagnosis of metastasis for 9 years and more than 13 years, respectively. We discuss a possible reason for this favorable course.

Case series

Case 1

Patient 1 was a 66 year old lady. She was operated because of rectal adenocarcinoma UICC stage I in 2003 and received a R0 resection. In the year 2005 she developed skin and hepatic

Abstract

2 cases of patients with remarkable survival time in stage IV rectal cancer are presented. Histopathological data attributable to malignant tissues may deliver possible reasons for the favorable course. Arguments to acknowledge the value of the modulation of the intra- and peritumoral microenvironment in the treatment of metastatic diseases are presented.

Keywords: long term survival; stage IV rectal cancer; peritumoral reaction; tumor microenvironment; macrophages; endothelial cells.

Abbreviations: FOLFOX: Fluorouracil, Leucovorin, Oxaliplatin; FOLFIRI: Fluorouracil, Leucovorin, Irinotecan; 5-FU: 5-Fluorouracil; VEGF: vascular endothelial growth factor; VEGF-R: vascular endothelial growth factor–receptor; ACE: angiotensin converting enzyme.

metastasis. The pathological analysis revealed a k-RAS wild type status. Following a R0 resection at both sites she was treated with FOLFOX4, which was stopped after 3 months time because of a polyneuropathy. One year later a lung metastasis appeared, and therapy was continued with bevacizumab-FOLFIRI, resulting in a mixed response. So chemotherapy was switched to cetuximab-irinotecan. This therapy was continued with short interruptions because of stable disease for a total application time of 12 months. Due to progression of lung metastasis therapy went on with bevacizumab-capecitabine for 6 months. Because lung metastases still were present and due to a palmar erythema of the hands therapy was changed to panitumab for a period of 6 months. However, lung metastases showed a progression which could not be stopped by a therapy with mitomycin–capecitabine.

Citation: Koch BA, Uflacker L, Tannapfel A. Long survival in metastatic rectal cancer: Due to modulation of the microenvironment?. *Japanese J Gastroenterol Res.* 2021; 1(1): 1002.

Bevacizumab–FOLFIRI was reintroduced over a period of 18 months, intermediately resulting in a partial remission. However, after few months metastasis progressed again, and therapy was changed to panitumumab-FOLFIRI for 12 months, unfortunately leading to dermal side effects. Since lung metastasis slowly progressed, therapy was switched to aflibercept-FOLFIRI for a period of 6 months. Finally, the patient developed a peritoneal metastasis. Lung metastasis showed a progression and chemotherapy was stopped. The patient died in 2014, 9 years after initial diagnosis of metastasis.

Case 2

Patient 2, aged 61 years, presented in 2008 with a rectal adenocarcinoma metastasising to the ovaries and to the peritoneum. She received a local R0 resection of the cancer of the the rectum and the adnexes and a R2 resection of a peritoneal metastasis. She was treated with bevacizunab-FOLFIRI for 3 months and continued afterwards with 5-FU and folinic acid for 8 months followed by capecitabine for 4 months. Initially, stable disease could be maintained, however, then a metastasis to the abdominal wall was detected and removed by a R0 resection. Chemotherapy was continued with capecitabine for 8 months. A second metastasis to the abdominal wall ocured followed by local irradiation. The molecular analysis revealed a K-RAS wild type status. 7 months later bilateral lung metastases were detected and therapy was performed by application of bevacizumab-FOLFOX for 6 months resulting in partial remission of the lung metastases. Therapy went on by treatment with cetuximab-FOLFIRI for 7 months followed by capecitabine for 16 months due to temporary stable disease situation. However, lung metastases started to progress again leading to two thoracotomies and removal of lung metastases. In the mean time the extended RAS analysis exhibited a N-RAS mutation type.

Therapies were performed by the application of bevacizumab-FOLFOX6 for 3 months, bevacizumab-5-FU and folinic acid for 11 months, and capecitabine for 10 months resulting in a stable diease situation in the lung. However, lung metastasis progressed again in the year + 9, and therapy was started with ramucirumab-FOLFIRI. The lung metastasis reacted with stable disease, however, an abdominal wall metastasis arose and was treated with local irradiation and capecitabine for 3 months. Because of further progression of the metastases in the lung and the abdominal wall treatment was continued with with ramucirumab-FOLFIRI and local irradiation of the abdominal wall resulting in a stabilisation at both sides. In the year +11 a cerebellar metastasis was detected and treated with excision and twice with irradiation. A therapy was started with tipiracil-trifluridine, which currently is going on. Although the patient is hampered by the multiple therapeutical modalities applied, and several metastases in brain and lung are detectable, she is still living and ready to continue with therapeutical interventions in the year +13 following the diagnosis of a stage IV rectal carcinoma.

Discussion

A survival time of more than 9 years in stage IV rectal cancer is remarkable. Since various factors are involved in the course and progress of metastatic disease the participation of factors beyond the tumor itself should be considered. The role of angiogenesis in cancer growth has been described many years ago [2]. The patients described here received several therapies with agents targeting both the tumor itself and cells in the tumor microenvironment. Often, in the intra- and peritumoral areas a dense infiltration with inflammatory cells are detected. Based on mmunohistological data it should be remembered that within the tumor microenvironment an increased amount of endothelial cells [3] and an intense infiltration with monocytes [4] have been demonstrated. In animal experiments it has been shown that the continuous inhibition of angiogenesis is able to block the progression of tumor growth [5]. In the human situation the use of antibodies directed against angiogenic factors and receptors such as VEGF and VEGF-R has proven its value in various tumor situations. When looking at colorectal tumors the application of substances such as bevacizumab [6,7], ramucirumab [8], and aflibercept [9] has revealed its efficacy. In most cases, these drugs are used in combination with antiangiogenic substances such as 5-FU [10], which is a component of FOLFOX and FOLFIRI, or capecitabine [11], which is a prodrug of 5-FU, or trifluridine-tipiracil, which contains an inhibitor of the enzyme thymidine phosphorylase [12] present in endothelial cells and macrophages [13]. All of these substances mediate strong antiangiogenic and macrophage blocking activities. Targeting the macrophage and endothelial compartment both supporting the progression of malignant diseases is worth to focus on and to evaluate the tumor growth modulating capacity of those cells. The approach of targeting macrophages and endothelial cells in combination is supported by the fact that both cell lineages carry common markers such as CD68 [14] and CD143 also known as ACE expressed both in/on endothelial cells and tumor infiltrating macrophages [15]. Since 5-FU, capecitabine, and tipiracil-trifluridine are part of several antineoplastic schemata and several combinations it may be difficult to determine the contribution of a single factor to the long term survival effect. It seems to be valuable to focus on the cell populations targeted by those drugs and on the cells involved in the progress of malignant diseases at certain stages of the course. It seems interesting to define the characteristics of those bystander cells contributing to the retardation of the progression of a metastatic disease and to achieve an at least limited chronification of an otherwise lethal disease.

Conclusion

In the concert of tumor growth supporting activities the action of macrophages and endothelial cells represents a very important contribution to the tumor growth driving mechanisms. It seems worthwhile to collect those cases whose course surpasses the known median overall survival time of the affiliated tumor entity, to look for the occurence of similarities in patients histories and treatment schedules, and to analyse whether secondary targets besides the tumor cell itself may play a role in the modification of

the course of a lethal disease. Researchers should be motivated to report those cases with a noticeable survival time significantly exceeding the median overall survival time of the affiliated tumor entity.

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